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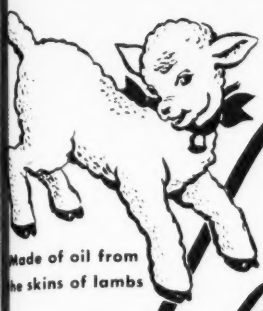

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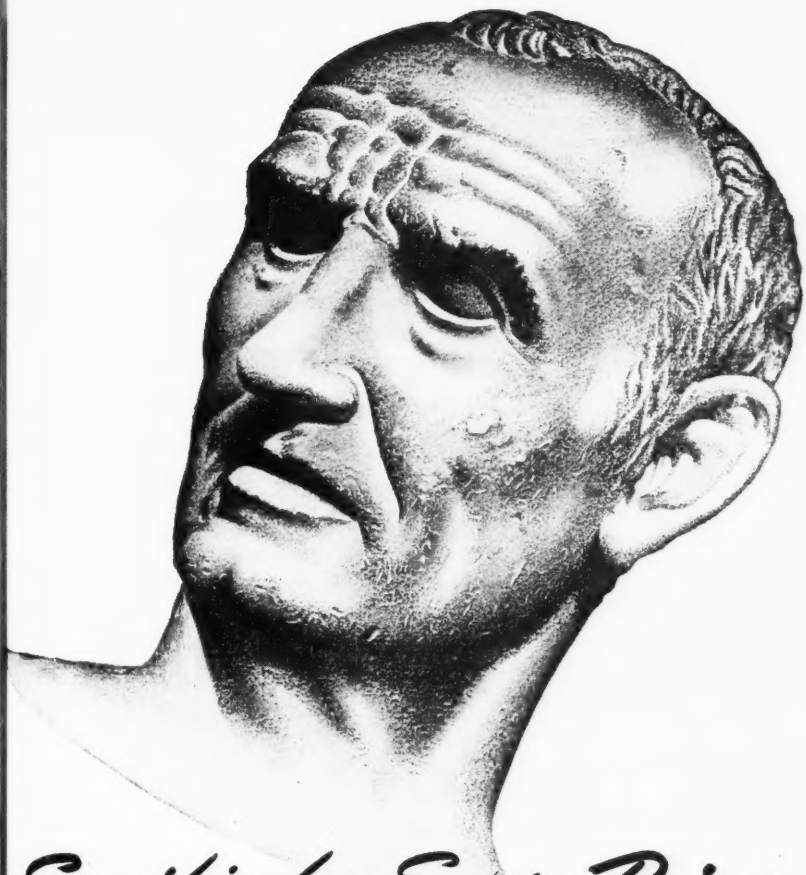

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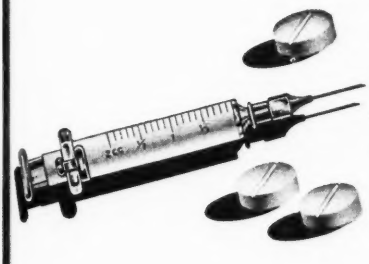

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1. Brewster, J. M., U. S. Naval Med. Bull. 49:1–11, January-February, 1949.

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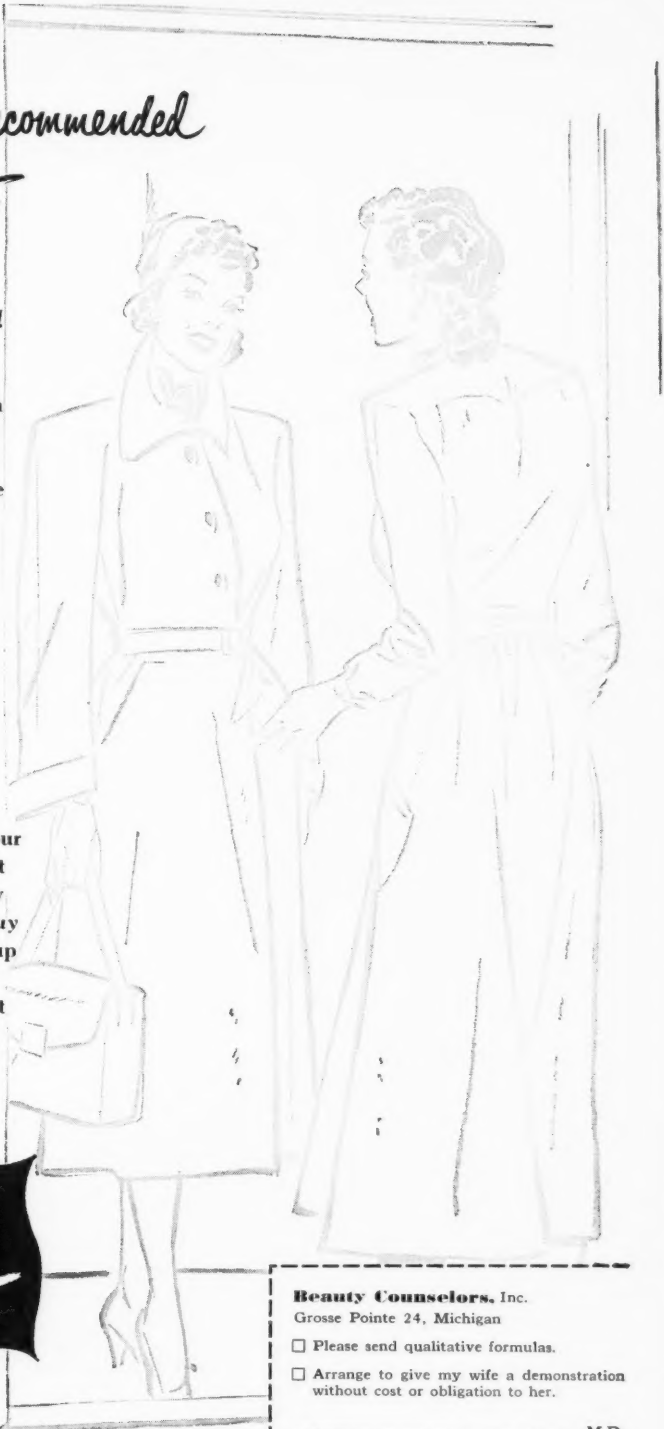

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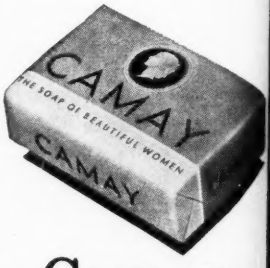

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[1]Encyclopaedia Britannica

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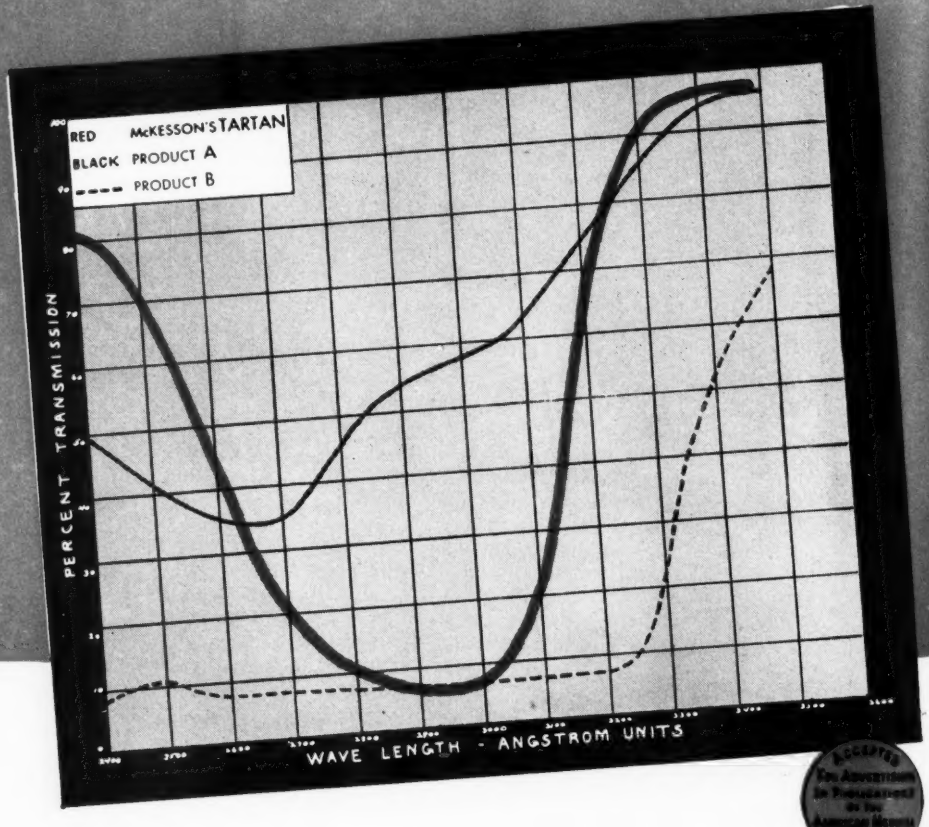

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Archives of Dermatology and Syphilology

VOLUME 59 JUNE 1949 NUMBER 6

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TREATMENT OF EARLY SYPHILIS WITH PENICILLIN INJECTION IN OIL AND WAX U.S.P.

Report of One Hundred and Fifty-Three Cases

LOUIS CHARGIN, M.D.

NATHAN SOBEL, M.D.

CHARLES REIN, M.D.

AND

THEODORE ROSENTHAL, M.D.

NEW YORK

IT IS NOW abundantly clear that penicillin is the most satisfactory antisyphilitic remedy so far developed. It is perhaps not more effective than arsenic given in intensive doses, but it is certainly safer, rapid in action and more readily administered. The best results thus far obtained have been with penicillin in aqueous solution.[1] However, this method of administration has two major disadvantages:

1. It requires hospitalization of the patient, and adequate bed capacity for the large number of patients requiring treatment is at present not available.

2. The financial outlay on the part of the patient, as well as the hospital, is often prohibitive.

It is therefore essential—indeed, imperative—that a satisfactory ambulatory method of therapy, one that is readily available to the patient as well as to the practitioner, be developed. The introduction of the absorption-delaying mixtures seems to meet the requirements. Penicillin injection in oil and wax U.S.P. is perhaps the most important and most widely used of the preparations introduced to date.

Read at the Sixty-Eighth Annual Meeting of the American Dermatological Association, Inc., San Diego, Calif., April 27, 1948.

This study was made possible by a grant-in-aid and materials from Bristol Laboratories, Inc., Syracuse, N. Y.; D. K. Kitchen, M.D., Medical Director.

From the Department of Health, City of New York, and the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, Dr. Marion B. Sulzberger, Director.

1. Arnold, R. C.; Mahoney, J. F.; Cutler, J. C., and Levitan, S.: Penicillin Therapy in Early Syphilis, J. Ven. Dis. Inform. **28**:241, 1947.

A number of studies dealing with the use of the injection in cases of early syphilis have already appeared.[2] These indicate that penicillin given in this form is a satisfactory means of treatment. However, physicians are still largely in ignorance of what schedule will furnish the optimal result and also of what dose, interval of injections, particle size and particular fraction should be used, or whether amorphous or crystalline penicillin is the better to use.

Thomas and associates,[2a] in a large series of cases, employed penicillin injection in oil and wax, a total of 4,800,000 units, administered in doses of 300,000 units twice a day, or 600,000 units once a day, for eight days. Similarly, Rauschkolb and Cole,[2b] in a smaller series, employed 600,000 units in a single injection given daily for eight days, for a total of 4,800,000 units. Although the results of Thomas far surpassed those of Rauschkolb, even Thomas' results fell short of those obtained with penicillin in aqueous solution. On the basis of clinical [3] as well as laboratory data [4] dealing with the principle of the time-dose relation in penicillin therapy, the suggestion was made that, with an extension of the time over which treatment is given, with use of the same, or even a smaller (divided) dose, a more satisfactory outcome could be achieved.

PRESENT INVESTIGATION

The present study was undertaken with the foregoing thought in view. Penicillin injection in oil and wax U.S.P., in doses of 300,000 units, was administered for sixteen consecutive days, except Sundays, for a total of 4,800,000 units. Thus the same total dose used by Thomas and by Rauschkolb was employed, but the daily dose was one-half theirs and the time element doubled.

Our study included 199 patients (table 1): 134 were male and 65 female; 47 were white persons and 152 were not. The ages varied from 16 to 68 years.

Injections were given once daily in the outpatient clinic during the morning hours. The treatment in no way interfered with the usual daily routine of the patients; all the 199 patients completed treatment. However, 46, or 23 per cent, were lost from observation, and this report, therefore, deals with the remaining 153 patients, which number represents 77 per cent of the original total.

The patients were not a selected group, except that each one suffered from early syphilis. Each person was subjected to a general physical examination

2. (*a*) Thomas, E. W.; Landy, S., and Cooper, C.: Rapid Treatment of Early Syphilis with Penicillin in Beeswax and Oil, J. Ven. Dis. Inform. **28**:19, 1947. (*b*) Rauschkolb, J. E., and Cole, H. N.: Treatment of Syphilis with Penicillin Injection in Oil and Wax, U. S. P.: Analysis of 175 Cases, to be published. (*c*) Romansky, M. J., and Rein, C. R.: Treatment of Early Syphilis with Calcium Penicillin-Oil-Beeswax, J. A. M. A. **132**:847 (Dec. 7) 1946.

3. McDermott, W.; Benoit, M., and DuBois, R.: Time-Dose Relationships of Penicillin Therapy: Regimens Used in Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **29**:345, 1945.

4. Eagle, H.; Magnuson, H. J., and Fleischman, R.: Effect of Method of Administration on Therapeutic Efficacy of Sodium Penicillin in Experimental Syphilis, Bull. Johns Hopkins Hosp. **79**:168, 1946.

and, without regard to abnormalities (such as cardiac or pulmonary disease), was given treatment. A full dose was used in all cases from the start except in 3 instances, in which, because of syphilitic laryngitis, smaller doses were given initially so that possible Herxheimer reactions of the larynx might be prevented, but the dose, being increased on subsequent injections, ultimately, even in these cases, reached 4,800,000 units in sixteen days.

Serologic tests of the blood were performed on all patients at both the beginning and the end of the treatment. However, on the patients with seronegative primary syphilis, tests were performed oftener in order to detect a possible rise in the titer during the treatment. Thereafter, on all patients, tests were performed at least monthly throughout the follow-up period. All patients were subjected to the following six titered procedures: Mazzini, Venereal Disease Research Laboratory cardiolipin, Kline exclusion, Rein-Bossak cardiolipin and Kolmer complement fixation tests and a cardiolipin complement fixation test.

TABLE 1.—*Distribution by Race and Sex of Patients Treated with 300,000 Units of Penicillin in Oil and Wax U.S.P. Daily for Sixteen Days* *

	Total	White Persons	Nonwhite Persons
Total	199	47	152
Male	134	37	97
Female	65	10	55

* No treatment on Sundays.

TABLE 2.—*Classification of the One Hundred and Fifty-Three Patients According to Diagnosis*

Original Diagnosis	Under Observation	
	Patients	Percentage
Seronegative primary syphilis	13	8.5
Seropositive primary syphilis	51	33.3
Secondary syphilis	83	54.2
Early latent syphilis	6	3.9

The patients were divided into the following groups (table 2):

1. Patients with seronegative primary syphilis, all proved by positive results on dark field examination.

2. Patients with seropositive primary syphilis, also proved by positive results on dark field examination, who had either a positive serologic reaction at the outset or an initially negative reaction which became positive during the first few days of treatment.

3. Patients with secondary syphilis, who had clinical evidence of early syphilis as well as positive serologic reactions.

4. Patients with early latent syphilis, who showed no clinical manifestations but had positive serologic reactions and a definite history indicating a recent infection.

The period of treatment was from February to July 1947, and the period of observation extended to April 1948. Thus the patients were observed for from eight to fourteen months.

When the clinical evidence of the disease had disappeared, which development was uniformly rapid in all cases, the further response to therapy was judged by the serologic reactions. As was stated, we performed a battery of six tests. In evaluating the results, however, we selected the Mazzini test in order that our evaluation could be compared on the same basis with the similar, although not identical, tests employed by Thomas, Landy and Cooper and by Rauschkolb and Cole. It was found that the Mazzini test as performed in our laboratory was

TABLE 3.—*Periods of Observation of Patients with Primary Seronegative Syphilis*

Months After Treatment	Number of Patients
1	..
2	..
3	..
4	..
5	..
6	2
7	4
8	..
9	2
10	3
11	2

TABLE 4.—*Time When Seronegativity Was Attained in Cases of Seropositive Primary, Secondary and Early Latent Syphilis*

Months After Treatment	Seropositive Primary Syphilis	Secondary Syphilis	Early Latent Syphilis	Total
Total	51	83	6	140
Became seronegative	47 (92%)	62 (74.7%)	4 (66.66%)	113
Remained seropositive or had clinical relapse	4 (8%—)	21 (25.3%)	2 (33.34%)	27
1	18	3	..	...
2	11	4	..	...
3	13	17	1	...
4	5	11	..	...
5	..	10	1	...
6	..	7	2	...
7	..	8	..	...
8	..	..	..	...
9	..	..	..	...
10	..	2	..	...
11	..	..	..	...

of similar sensitivity and specificity to that of the Kahn test performed by Thomas and his associates.

Table 3 presents a detailed picture of the observation status of the 13 seronegative patients. They were followed for a period of six to twelve months. All remained seronegative throughout.

Of 51 patients with seropositive primary syphilis (table 4), 47 (92.2 per cent) became seronegative and 4 (8 per cent), of whom 2 (4 per cent) eventually showed a clinical relapse, remained seropositive. All 47 became seronegative by the end of four months.

Of the 83 patients with secondary syphilis, 62 (74.7 per cent) became seronegative and 21 (25.3 per cent), of whom 4 (4.8 per cent) eventually showed a clinical relapse, remained seropositive. All the 62 became seronegative within ten months.

Patients with secondary and early latent syphilis represented 60 per cent of the total. They came under care much too late for the best results in therapy, for these persons not only showed less satisfactory results (in 74.7 per cent as against 92 per cent) but took much longer to become seronegative.

TABLE 5.—*Serologic Drop in Titer in Treated Patients Still Under Observation*

Diagnosis	Titer at Onset	Titer at Present	Duration of Observation, Months
Seropositive primary syphilis (2 cases)			
1	64	4	10
2	32	4	10
Secondary syphilis (17 cases)			
3	32	3	8
4	16	2	7
5	128	2	7½
6	128	2	9½
7	256	1	9½
8	64	2	10½
9	512	64	8
10	64	4	10
11	128	8	9
12	64	64	10
13	256	4	7
14	128	4	8
15	128	1	7
16	64	2	12
17	320	19	7
18	288	10	7
19	896	1	6
Early latent syphilis (2 cases)			
20	32	3	8
21	32	8	8½

This situation is illustrated by the fact that 92 per cent of the patients with seropositive primary syphilis became seronegative at the end of the fourth month, while of the patients with secondary syphilis, during the same period, only 56 per cent became seronegative. Moreover, the rate of relapse was higher in the secondary group.

Of the 6 patients with early latent syphilis, 4 (66.7 per cent) became seronegative.

Table 5 presents an analysis of the cases in which there was still a positive serologic reaction to some degree after an observation period of up to ten and a half months. Some would regard these cases as representing therapeutic failures. But do they? In an examination of the table, it will be observed that, except in case 12, a pronounced reduction in serologic titer was obtained, indicating at least a satisfactory downward trend toward seronegativity. Recent experience

teaches that in many such cases the disease eventually fades out completely, taking as long as two years to do so. While in a number of cases the positive serologic reaction may persist and a clinical relapse may actually occur—the case hence being classified as a therapeutic failure—it is reasonable to expect that these cases will be more than counterbalanced in number by those in which the positive reaction will fade out, this tendency thus further increasing the percentage of cases with a satisfactory outcome.

Of the 6 patients who showed clinical relapses (table 6), 2 originally had had seropositive primary infections and 4 had secondary syphilis. They are all regarded as representing therapeutic failures, although 2 may have had reinfections, if judged by the less severe criteria of reinfection. Of the patients with seropositive primary infections, 1 had a relapse four months after treatment and may have had a "ping-pong" reinfection,

TABLE 6.—*Number of Months after Treatment that Patients Showed Clinical Relapse or Reinfection*

Months After Treatment	Original Diagnosis	
	Seropositive Primary Syphilis	Secondary Syphilis
.....	2	4
1.....	..	1
2.....	..	..
3.....	..	1
4.....	1	..
5.....	..	..
6.....	..	..
7.....	..	1
8.....	1	1

and the other, eight months after treatment. This patient gave a history of repeated exposures and was seronegative for four months prior to the appearance of the new sore. In the 4 patients with secondary syphilis, 1 relapsed one month; 1, three months; 1, seven months, and 1, eight months after treatment.

All patients who showed clinical relapses were retreated. After the second course of treatment, 3 became seronegative; the other 3 are still seropositive, although there is a drop in titer in the serologic tests.

REACTIONS

Two types of penicillin injection in oil and wax U.S.P. were employed in treatment, the original viscous preparation and the recently introduced fluid suspension. One hundred patients were treated with the former and 99 with the latter. It is of interest to observe that only the viscid preparation produced the more intense reactions. Six patients showed various grades of severe reactions, consisting of pronounced urticaria, varying from small to giant lesions, often accompanied

with arthralgia, and in 1 case by erythema-nodosum-like lesions on the extremities, all accompanied with varying grades of fever. Mild reactions, consisting of itching, were observed in 10 of the patients. With the fluid suspension the only reaction observed was itching, in 10 patients. One patient had jaundice one month after treatment. He was hospitalized, but extensive studies failed to reveal a relation of the jaundice to therapy, the final diagnosis being infectious hepatitis. In spite of reactions, treatment was continued and completed, always, however, with the administration of tripelennamine hydrochloride (pyribenzamine hydrochloride®).

TABLE 7.—*Summary and Comparison of Results of Therapy with Penicillin in Oil and Wax*

	Thomas and Associates [2a] (300,000 Units Twice Daily, or 600,000 Units Once a Day, for Eight Days; Total Dosage, 4,800,000 Units)		Rauschkolb and Cole [2b] (600,000 Units Daily for Eight Days; Total Dosage, 4,800,000 Units)		Chargin and Associates (300,000 Units Daily for Sixteen Days *; Total Dosage, 4,800,000 Units)	
	Number	Percentage	Number	Percentage	Number	Percentage
Seronegative primary syphilis....	59	100.0	10	100.0	13	100.0
Remained seronegative.....	55	93.2	9	90.0	13	100.0
Had relapse or reinfection...	4	6.8	1	10.0	0	0.0
Seropositive primary syphilis....	159	100.0	40	100.0	51	100.0
Became seronegative.....	137	86.2	24	60.0	47	92.2
Remained seropositive.....	2	1.2	8	20.0	2	4.0
Had relapse or reinfection...	20	12.6	8	20.0	2	4.0
Secondary syphilis.....	372	100.0	57	100.0	83	100.0
Became seronegative.....	233	62.6	17	29.8	62	74.7
Remained seropositive.....	98	26.4	19	33.3	17	20.5
Had relapse or reinfection...	41	11.0	21	36.9	4	4.8
Early latent syphilis.....	0	....	9	100.0	6	100.0
Became seronegative.....	..	....	0	0.0	4	66.7
Remained seropositive.....	..	....	3	33.3	2	33.3
Had relapse or reinfection...	..	....	6	66.7	0	....

* Exclusive of Sundays.

Pretreatment lumbar puncture was not performed on any of our patients, since it is well established that abnormalities found at this time bear no relation to post-treatment abnormalities. For obvious reasons, we have intentionally postponed performing lumbar puncture until about a year after therapy, and hence at this time can report on observations concerning only 90 cases. The spinal fluid was found to be normal in all except 1 instance, that of a patient with secondary syphilis, in which the count was 40 cells per cubic millimeter, while the other findings were normal. This patient will, of course, be followed further.

In table 7 a summary of our results and a comparison with the results of the two other studies previously mentioned is presented. It

will be observed that in cases of primary seronegative syphilis the results are outstanding, approaching a satisfactory outcome for 100 per cent of the patients. In this type of syphilis, treated by any of the schedules under consideration, results are highly satisfactory and there is no therapeutic problem. Of the patients with seropositive primary syphilis, the results obtained with the eight day schedule were satisfactory for 60 per cent, as reported by Rauschkolb, and for 86.2 per cent as reported by Thomas. In our series, with the sixteen day schedule, results were satisfactory for 92 per cent of the patients. Of the patients with secondary syphilis, the results obtained with the eight day schedule were satisfactory for 29.8 per cent in Rauschkolb's investigation, and for 62.6 per cent in Thomas'. In our series, results were satisfactory for 74.7 per cent of the patients. The base line for satisfactory results in treatment of secondary syphilis, as published by the Cooperative Rapid Treatment Center Group, is a successful outcome for about 60 per cent of the patients. We feel, consequently, that treatment by our schedule gives definitely superior results. The number of patients with early latent syphilis treated by Rauschkolb and ourselves is too small to warrant analysis.

It may be open to question whether the better showing made by the sixteen day treatment schedule is real, or only apparent because of the somewhat differing serologic tests employed in the three studies. To overcome this difficulty, a standard serologic test that will be employed by all participants in future studies will have to be agreed on.

SUMMARY

A series of 199 patients with early syphilis were treated while ambulatory by a sixteen day schedule employing 4,800,000 units of penicillin in oil and wax. Of the original series, 153 patients, or 77 per cent of the total, form the basis of this study; 46 patients (23 per cent) were lost from observation.

Our results are compared with those in two eight day schedules employing 4,800,000 units of penicillin in oil and wax.

Our longer schedule appears to show more satisfactory results for all categories.

With the sixteen day schedule, the results with primary seronegative and seropositive syphilis are eminently satisfactory.

With secondary syphilis the results are less striking.

Further comparative studies, employing a uniform serologic test for evaluating the cases, are needed.

1 West Eighty-Fifth Street (Dr. Chargin).

124 East Fortieth Street (Dr. Sobel).

580 Fifth Avenue (Dr. Rein).

1 West Ninety-First Street (Dr. Rosenthal).

ABSTRACT OF DISCUSSION

DR. HERMAN BEERMAN, Philadelphia: Drs. Chargin and Rein and their colleagues have presented a straightforward statement of careful observation on a problem which is paramount in today's syphilology, namely, the development of a rational and effective basis for ambulatory treatment of early syphilis. Furthermore, they have presented evidence which tends to reaffirm the principle, long established for arsenical and heavy metal therapy, that the time (duration) is as important as the amount (mass) of treatment, if not more so. They have, in addition, indicated that an ambulatory regimen of treatment for early syphilis need not, even if prolonged, have the result that a high proportion of patients do not complete the prescribed treatment of schedule.

By employing a system of therapy which differs from that of two previous studies only in the fact that the same total dose was administered in twice the time, Chargin and his group have materially increased the good results as far as immediate clinical effects, and particularly the serologic reactions, are concerned. As in all short term studies, these results must be reevaluated over a longer period than eight to fourteen months. However, the trend, as reported here, is significant. One is tempted to ask whether the present results may be superior not because of the time factor alone but because so-called liquid penicillin was used in about half of the cases. Liquid preparations of crystalline penicillin of large particle size have been shown by Dowling and his co-workers to be most satisfactory. (Dowling, H. F., and others: "Liquid" versus "Solid" Penicillin in Oil and Wax: Effect of Particle Size and Type of Penicillin, J. A. M. A. **135**:567 [Nov. 1] 1947.)

There is no longer reason to doubt the relative effectiveness of the penicillin in oil and wax mixture when compared in like amount with aqueous solutions of the drug. This effectiveness has been demonstrated in early syphilis by various investigators, and our group at the Institute for the Study of Venereal Disease, University of Pennsylvania, has even shown this preparation to be highly useful in treatment of early syphilis of pregnancy, a phase of the disease in which good results are available with a certain degree of finality in a relatively short time (months after delivery) (Ingraham, N. R., Jr., and others: Treatment of Syphilitic Pregnant Woman with Penicillin in Oil-Beeswax: Comparison with Results Obtained Using Aqueous Sodium Penicillin, *J. Ven. Dis. Inform.* **28**:155, 1947). The main problem therefore is: Can a satisfactory ambulatory system of treatment be devised which involves prolongation of time and yet yields a high percentage of cases of completed treatment and good case holding? Chargin and his group, obviously having employed excellent case-holding methods, have demonstrated that the problem can be met by holding 77 per cent of their patients for from eight to fourteen months. That even greater prolongation of time is possible without significant loss of cases is illustrated by our experience with a voluntary ambulatory outpatient series, composed predominantly of Negroes, at the Institute, under the auspices of the National Institute of Health, in which we administered 18,000,000 units of penicillin in oil and wax in ten weeks (thirty doses of 600,000 units each) or 9,000,000 units in fifteen days (fifteen doses of 600,000 units each). In the first group, largely because of the good follow-up efforts of our field director, Miss Jane Taylor, and her staff, 34 of 38 patients (90 per cent) completed treatment (12 of these without a lapse and 18 with one or two lapses). In the fifteen day schedule, all 35 have finished the prescribed treatment, 32 of these on scheduled time.

Although the value of the study by Dr. Chargin and his collaborators is not seriously diminished by the fact that most studies employing penicillin now use the Kahn quantitative test, it is regrettable that this group did not follow suit. On the other hand, present quantitative procedures are in reality mere approximations and are not to be taken at their face value for interlaboratory comparisons of results. We agree that a standard laboratory procedure is needed; in fact, if all factors are to be adequately controlled, the performance of all the tests for the various studies by a central laboratory is to the point.

DR. JOHN E. RAUSCHKOLB, Cleveland: It is with considerable interest that I listened to the presentation, because I realize that it is a continuation of discussion of the method which was presented to this association last year. A few points as to variation: There is no doubt that the time relation has a large influence on the efficiency of penicillin in oil and wax of the same amount given over different periods of time. Our dosage was 600,000 units once a day for eight days. Our results were comparable. We observed one relapse. In the secondary stages, results were disappointing. Probably this increase in the percentage of failures was due to our critical attitude, as we considered a failure any case in which there was a clinical relapse and also any case in which the titer did not come down. In the small number of cases of latent syphilis we observed, our results were disappointing. All the foregoing points substantiate the idea that penicillin is a powerful drug, comparable to the arsenical compounds, particularly efficient and workable in very early stages of syphilis but losing effectiveness as the disease progresses to latent stages. This fact also appears in Dr. Chargin's results. The time to use penicillin is in the very early stages of the disease. We have continued, with some modification, our therapy since June 1947.

We have reduced our administration of penicillin to 400,000 units per day, on an eight day basis, and have added to that dosage ten injections of oxophenarsine hydrochloride (mapharsen®) and ten injections of a bismuth preparation. We have been able to follow a great number of cases. We have at no time seen any relapses or recurrences after that type of therapy. I will say that the time since treatment is still less than a year for these cases, but you must remember that most of the relapses and reinfections in all the old series came within four to eight months after therapy. I enjoyed this presentation because it indicates the right method for the use of penicillin.

DR. A. BENSON CANNON, New York: It might be of interest to recite my associates and my experience at Vanderbilt Clinic in the treatment of early syphilis with penicillin in oil and wax in combination with oxophenarsine hydrochloride. We have 92 patients who have neither clinical nor serologic evidence of the disease and who have been observed for from six to thirty-six months. The treatment consisted of ten injections of 600,000 units of penicillin in oil and wax, given daily except on Saturdays and Sundays, and 60 mg. of oxophenarsine hydrochloride for six injections, given every other day. In 1 case it required twenty-two months for us to obtain an entirely negative serologic reaction, and in a second case eleven months elapsed before the Wassermann reaction was negative. Our results with penicillin in oil and wax were just as good as those obtained by our treatment with an equal amount of penicillin given every three hours for seven and one-half days in combination with oxophenarsine hydrochloride. We have studied the penicillin levels determined after each injection and have found that 300,000 units of the injection in oil and wax gives a therapeutic blood level for from six to nine hours. In the last few months we have been using procaine penicillin in oil and have found that 300,000 units of the mixture will give a therapeutic level for as

long as twenty-four hours. In the majority of cases 600,000 units maintains a therapeutic level for at least forty-eight hours, and 900,000 units, for seventy-two hours or ninety-six hours. These findings enable us to give our injections of penicillin every second day, in doses of 600,000 units, or every third day when 900,000 units are used. This method has resulted in a great saving of time and inconvenience to the patient and the use of a smaller amount of penicillin. It appears to me that the only scientific way to determine the proper dose and intervals between treatments is to study the blood levels after each injection. I have been much interested in Dr. Chargin's excellent paper and am surprised that the results are as good as they are, considering that the patients were probably without therapeutic blood levels of penicillin for at least half the period of treatment.

DR. J. LAMAR CALLAWAY, Durham, N. C.: The results as presented here are at variance with those presented by the cooperating clinics working with the National Institute of Health and the United States Public Health Service. It has been shown statistically that a longer period is no better than a shorter period, as long as the total dose is adequate. It has been shown, also, that a combination of arsenic and bismuth preparations with penicillin in doses so far employed is not better than aqueous penicillin alone or penicillin in one of the absorption-delaying vehicles. It appears that penicillin in one of the absorption-delaying vehicles is as efficacious in treatment as is aqueous penicillin. It is certainly more practical to treat and hold a patient for eight days than for sixteen days.

DR. CHARLES R. REIN, New York: In this study, all the specimens of serum were subjected to a battery of six quantitative serologic tests. It should be pointed out, however, that only the Mazzini test was used in determining the serologic response to penicillin therapy. This test was selected because it more closely approached the sensitivity of the Kahn standard test employed by Thomas and his associates in their study, thereby permitting a more satisfactory comparison of serologic results.

There is now available a new penicillin preparation (procaine penicillin G in a 2 per cent solution of aluminum monostearate), which is being investigated under the direction of Dr. Thomas at Bellevue Hospital. A single injection of 300,000 units contained in 1 cc. will produce adequate blood levels of penicillin for four days in the majority of patients. It is quite possible that with the use of this new product one may be able to obtain excellent results in the treatment of early syphilis by the administration of 1 cc. once a week for four weeks. It would not be necessary to hospitalize patients or to give injections more frequently than once or twice a week.

SCLEROMA

Review of Literature and First Report of Multiple Familial Occurrence in the United States

PAUL R. KLINE, M.D.
NEW YORK
AND
EDWIN R. BRODY, M.D.
YOUNGSTOWN, OHIO

SCLEROMA is a specific chronic granuloma localized in the rhinopharyngeal tract, involving the tissues of the nose, pharynx, larynx, trachea and bronchi.

The disease was first described in 1870 by von Hebra,[1] a Viennese dermatologist. It undoubtedly had existed in eastern Europe for many years prior to that time, as evidenced by the fact that wax models of this disease made in 1840 were on exhibit at the Museum of the History of Medicine in Cracow, Poland. These had been presented by Bierkowsky [2] as examples of carcinoma. Von Hebra himself expressed the belief that this condition, which he termed rhinoscleroma (hard nose), was a granulomatous sarcoma or an atypical form of syphilis. Geber,[3] von Hebra's assistant, stated the opinion that it was a specific entity. In 1876, Mikulicz [4] reported the presence of peculiar foam cells seen in histologic studies. In the same year Gerhardt [5] first described a case of laryngeal scleroma. In 1882 von Frisch [6] and Pellizzari isolated an encapsulated diplobacillus, the "bacillus rhinoscleromatis," in the nasal secretions, which organism they felt to be the etiologic agent.

The most complete summary of the disease to date was compiled in 1932 at the Second International Congress of Otorhinolaryngology at Madrid, Spain, at which time 2,361 cases were collected for discussion. At this meeting it was officially decided that the name rhino-

From the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital.

1. von Hebra, F.: Wien. med. Presse **11**:445, 1870.

2. Bierkowsky, cited by Szmurlo, J.: Rapports de Congrès international d'oto-rhino-laryngologie, 1932, p. 34.

3. Geber, E.: Arch. f. Dermat. u. Syph. **4**:491, 1872.

4. Mikulicz, F.: Arch. f. klin. Chir. **2**:485, 1876-1877.

5. Gerhardt, cited by Mikulicz.[4]

6. von Frisch, A.: Wien. med. Wchnschr. **32**:969, 1882.

scleroma, coined by von Hebra, should be changed to the more inclusive term, scleroma.

INCIDENCE

When first described, scleroma was apparently limited to areas in central and southeastern Europe. Poland and Russia were the countries of greatest incidence. In 1890 Cornil and Bobes [7] reported that they had not seen any cases of scleroma in the extensive dermatologic service of the St. Louis Hospital in Paris, then the largest in the world.

TABLE 1.—*Cases of Scleroma in Native Americans*

Author	Year	Patient		Nativity	Location of Lesion
		Sex	Age		
1. Wende [10]	1895	M	11	Buffalo	Right naris and nasopharynx
2. Lieberthal [11b]	1911	F	26	United States	Naris, lip and pharynx
3. Watkins [11c]	1921	M	23	Baltimore	Trachea
4. Wood [11d]	1925	M	24	New Jersey	Nose, pharynx and larynx
5. O'Leary and Montgomery [11e]	1927	M	26	Pennsylvania	Nose, pharynx and larynx
6. Canfield [11f]	1933	F	17	Michigan	Nose, pharynx and larynx
7. Helwig and Jaime [11g]	1933	M	20	Kansas	Larynx
8. Stout [11h]	1934	M	25	United States	No lesion; nasal crusting and discharge
9. Alderson [11i]	1937	F	29	California	Nose, lip and hard palate
10. Simpson and Ellis [11j]	1939	F	41	Greenville, S. C.	Nose
11. Cunning and Guerry [11k]	1942	M	21	Perth Amboy, N. J.	Nose, pharynx and larynx
12. Cunning and Guerry [11k]	1942	M	34	Brooklyn	Nose, pharynx and larynx
13. Kline and Brody	1948	F	41	Pennsylvania	Nose

Wars have been largely responsible for the spread of scleroma, since many European armies during the past century were composed principally of Russian and Polish soldiers. During World War I, scleroma spread rapidly. There was a considerable displacement of the civilian population, and, as armies and prisoners invaded other countries, scleroma began to appear in areas where previously it had not been known to exist. There was a notable increase in cases in Prussian Silesia, where Russian prisoners had been quartered. In addition, amelioration of traveling facilities since the turn of the century resulted in a large migration of these Slavic peoples to other parts of the world. Cases multiplied in Africa, Asia and India. Today, therefore, the incidence of scleroma is nearly worldwide. There are

7. Cornil and Bobes, cited by Gottheil, W.: J. Cutan. Dis. **35**:269, 1917.

relatively few countries where cases have not been reported. The disease has been seen in such geographically distant areas as Siberia, Sumatra, Sweden, South America and Australia. Recently Reyes [8] reported a study of 200 cases seen in El Salvador, Central America.

In the United States the first reported case of scleroma was presented by Jackson [9] in 1893 before a class of medical students at the Women's Medical College in New York. The first case occurring in a native-born American was reported by Wende [10] in 1893. To date and including the cases mentioned in this paper, there have been 102 cases reported in the United States. Of this number, 13 cases have occurred in native-born Americans (table 1).[11] Some of these patients had been abroad at some time during their lives, while others had never been outside the continental borders of the United States. The disease has been reported to occur more frequently in women. However, in the cases reported in native-born Americans, 8 have occurred in men and 5 in women. The ages in this group of native-born persons varied from 11 to 41, with 57 per cent of the cases occurring between the ages of 20 to 30 years. The disease usually begins in early adult life, although it may occur in children, as well as in those past middle age. Of the 89 immigrants in whom cases were reported, 42 were born in Russia or Poland, 10 were born in Australia, 7 in Mexico, 5 in Galicia, 5 in Italy and the remaining 20 in Hungary, Bohemia, Ruthenia, Ireland, Germany, Rumania, El Salvador, Yugoslavia, Guatemala and England.

This is the first report of the multiple occurrence of scleroma in the same family in the United States. Since 1918 the disease has been considered a contagious one, but as yet no definite conclusion has been reached as to the degree of contagiousness. It is definitely

8. Reyes, E.: Rhinoscleroma: Observations Based on Study of Two Hundred Cases, Arch. Dermat. & Syph. **54**:531 (Nov.) 1946.

9. Jackson, G. T.: J. Cutan. & Genito-Urin. Dis. **11**:381, 1893.

10. Wende, G. W.: Buffalo, M. J. **35**:642, 1895.

11. (*a*) Wende.[10] (*b*) Lieberthal, D.: J. Cutan. Dis. **29**:638, 1911. (*c*) Watkins, S. S.: Surg., Gynec. & Obst. **33**:45, 1921. (*d*) Wood, G. B.: Tr. Am. Laryng. A. **47**:87, 1925. (*e*) O'Leary, P., and Montgomery, H.: Rhinoscleroma, Arch. Dermat. & Syph. **16**:791 (Dec.) 1927. (*f*) Canfield, N.: Ann. Otol., Rhin. & Laryng. **42**:903, 1933. (*g*) Helwig, F. C., and Jaime, N.: Laryngeal Scleroma in Native Missourian: Report of Case, Arch. Otolaryng. **18**:310 (Sept.) 1933. (*h*) Stout, P. S.: Laryngoscope **44**:142, 1934. (*i*) Alderson, H. E.: Rhinoscleroma: Report of Case, Arch. Dermat. & Syph. **36**:1018 (Nov.) 1937. (*j*) Simpson, C. A., and Ellis, F. A.: Rhinoscleroma: Report of Two Cases, ibid. **39**:503 (March) 1939. (*k*) Cunning, D. S. and Guerry, D. P., III.: Scleroma, Arch. Otolaryng. **36**:662 (Nov.) 1942. (*l*) Kline, P. R., and Brody, E. R.: Present Study.

infectious. Belinoff,[12] in 1932, reported that while the disease had been acquired by many Bulgarian merchants and laborers going into Russia, Rumania, Poland and Czechoslovakia, not one had transmitted it to his family. On the other hand, Lasagna[13] of Italy recorded 15 Italians with the disease, all of whom were members of the same family and the majority of whom lived in the same house. Reyes,[5] in El Salvador, reported an instance of 2 brothers having scleroma, one acquiring the disease four months after the other. This was the only instance of multiple occurrence in the same family in the 200 cases reported by him.

Scleroma is not hereditary. Poverty, vitamin deficiencies and lack of personal hygiene appear to be predisposing factors. The majority of the cases occur in persons in the lower social strata, especially in countries where crowded living conditions compel close contacts between scleromatous and healthy persons.

ETIOLOGY

The exact etiologic agent of scleroma is disputed. Most authorities have expressed the belief that the causative organism is Klebsiella rhinoscleromatis (the von Frisch bacillus). It is a short, ciliated, encapsulated, aerobic, gram-negative bacillus, apparently related to the Klebsiella ozaenae and Klebsiella pneumoniae (Friedländer) group of organisms. It is 2 to 8 microns in length. It can be grown on agar, gelatin and potato, as well as in broth and milk. On human blood agar it develops colorless, mucoid colonies. On carbohydrate mediums, there is formation of acids but no gas. Gelatin is not liquefied. The bacillus forms a pellicle in broth; litmus milk is acidified and clotted. Nitrates are reduced to nitrites. The organism is found in stained tissues and nasal secretions.

The method of transmission of this disease is unknown. Attempts at inoculation in human beings by injection of scleromatous liquid into cheeks and ears and by insertion of tampons into the nasal cavity and even autoinoculation by subcutaneous implantation of scleromatous tissue have failed to produce the disease. Stepanow, Kraus and Šercer[14] inoculated white mice and succeeded to the extent of producing infiltrations at the site of inoculation which histologically resembled the picture of scleroma. However, the disease itself has not been produced in animals. Koch's postulates have therefore not been fulfilled. Fur-

12. Belinoff, S.: Epidemiology of Scleroma, Arch. Otolaryng. **18**:398 (Sept.) 1933.

13. Lasagna, F.: J. Laryng. & Otol. **40**:369, 1925.

14. Šercer, A.: Experimental Pathology of Scleroderma, Arch. Otolaryng. **18**:395 (Sept). 1933.

thermore, strains of the other encapsulated bacilli found in the nose (K. pneumoniae and K. ozaenae), which possess similar biochemical characteristics, have caused previous confusion as to the specificity of K. rhinoscleromatis.

It has been shown that an intracutaneous test with K. rhinoscleromatis in scleromatous patients has produced a positive reaction, consisting of an erythematous lesion several centimeters in diameter, whereas intracutaneous tests with K. pneumoniae and K. ozaenae have produced either a slight or no reaction. Moreover, serologic complement fixation and agglutination tests have further confirmed the specificity of K. rhinoscleromatis. The organism has also been cultured and a vaccine prepared by Ghosh [15] at the Medical School for Tropical Diseases, in Calcutta, India.

TABLE 2.—*Cases of Scleroma Occurring in the United States*

Location of Lesion	Number of Cases
Nose	25
Nose and pharynx	5
Nose, pharynx and larynx	15
Nose and mouth	2
Nose, lip and hard palate	1
Pharynx	0
Larynx	7
Pharynx and larynx	1
Nose and larynx	9
Trachea	1
Hard and soft palate, pharynx and trachea	1
Nose, soft palate and trachea	1
Nose, pharynx, larynx and trachea	2

CLINICAL COURSE

Scleroma begins insidiously, usually in the nasal septum or alae and progresses by peripheral extension. Lesions have involved the nose, nasopharynx, larynx, trachea and bronchi, with occasional extension occurring to adjacent structures, such as the lips, tongue, uvula, soft palate, orbit, lacrimal passages, eustachian tubes and tympanic cavity. The structures affected in cases reported in the United States are summarized in table 2. This table shows that of the cases reported, there were 34 per cent with involvement of the nose alone; 20 per cent seen in the nose and pharynx, 12 per cent observed in the nose and larynx and 9 per cent involving the larynx alone. It would seem, therefore, that the sites most frequently primarily involved are the nose and the larynx. Nothing is known as to the manner in which the disease is acquired.

15. Ghosh, N.: Personal communication to the author.

In the nose, scleroma is most frequently localized about the septum, alae, vestibule or posterior nares, and in the pharynx, about the uvula, faucial pillars and posterior surface of the soft palate. In the larynx it is usually found in the subglottal region, and, in the trachea, in the upper part near the larynx. Bronchial involvement was reported by Jaffé.[16] The disease may appear diffuse in one area and circumscribed elsewhere. The bony and cartilaginous structures remain unaffected. Ulcerative lesions, while uncommon in Europe, are commonly seen in the Western Hemisphere. They are believed to develop as a result of pressure necrosis and secondary infection. There is no systemic involvement. The onset is insidious, and the course is chronic and protracted.

There are apparently four stages of the disease:

1. *Catarrhal Stage.*—The disease appears as an atrophic type of rhinitis, in which atrophy of the nasal mucosa occurs. Nasal discharge is accompanied by grayish crust formations, which extend along the mucosa of the pharynx, larynx and trachea. There is diffuse infiltration of the subcutaneous tissues of the nose, nasopharynx and pharynx. The infiltrated mucosa becomes indurated, and atrophy of the cutaneous structures occurs. Infiltrations of the nasal vestibule and septum effect partial blocking of the nostrils. Similarly, stenosis occurs in the subglottic laryngeal space. Until this development the patient has few, if any, subjective symptoms.

2. *Localized Nodular Stage.* — Circumscribed nodules begin to develop, either singly or in groups, varying in size and consistency. Confluence and enlargement of these lesions produce mechanical obstructions in the affected area. In this stage the rhinitis gradually disappears. Localization of the infiltration occurs in the nose or larynx.

3. *Diffuse Nodular Stage.*—At this stage there occurs a progressive hardening and thickening of the nodules, with extension of the infiltration and invasion of surrounding structures. Diffuse involvement of the nasal walls, with enlargement of the alae and concomitant swelling of the upper lip, frequently results in gruesome facial deformities. Similar infiltrative changes involve the gingiva, tongue, soft palate, nasopharynx, pharynx and larynx.

4. *Cicatricial Stage.*—As the disease progresses and a terminal stage is reached, thick cicatrices replace the scleromatous infiltrations, this development causing additional deformity of the affected structures, as well as still further diminution of function.

16. Jaffé, R. H., in discussion on Crowe, S.: Rhinoscleroma of the Larynx and Pharynx in Two Immigrants, Arch. Path. **5**:1125 (June) 1928.

SYMPTOMS

Symptoms are largely the result of mechanical obstruction and impairment of function. Hoarseness may be the first noticeable symptom of laryngeal scleroma. Subsequently, coughing, changes in intonation, dyspnea and finally asphyxia develop. With nasal scleroma epistaxis is common, and rhinitis, respiratory difficulties and anosmia occur. The patient suffers loss of appetite and loss of weight, and cachexia eventually ensues. There are no constitutional symptoms. Involvement of the eustachian tube and the middle ear may produce partial deafness. Invasion of the lacrimal apparatus may result in persistent lacrimation and ectropion. Infiltration of the gingiva and atrophy of the alveolar processes may cause the teeth to fall out. Pharyngeal stenosis and thickening of the tongue produce difficulties in speech and pronounced dysphagia.

MICROSCOPIC APPEARANCE

Scleroma presents a definite, though not pathognomonic, microscopic picture. Two distinct elements are noted: the Mikulicz cell and the Russell, or Unna, bodies.

1. *The Mikulicz Cell.*—This is a large, vacuolated foam cell considered to originate from degenerated plasma cells or degenerated connective tissue cells. It varies from 50 to 100 microns in diameter. The cytoplasm is granular and stains poorly. The nucleus is small, pyknotic and eccentrically placed. Scattered in and around these cells, the gram-negative K. rhinoscleromatis is found. The Mikulicz cell is seen also in glanders, leprosy and bubonic plague.

2. *Russell-Unna Bodies.*—These are elliptic hyaline cells 20 to 40 microns in diameter, which also are believed to represent degenerated plasma cells. They take a deep stain with hematoxylin and eosin. These cells are likewise found in such other chronic granulomas as the lesions of tuberculosis, syphilis, leprosy and certain filtrable virus diseases and in various malignant neoplasms.

The histologic aspects vary with the stage of the disease present. Early phases show an acanthosis, with downward growth of the rete pegs. There is a pseudoepitheliomatous hyperplasia, hyperkeratosis and parakeratosis. In the corium, fluid accumulates and there is a thinning of the connective tissue and the elastic tissue, with hydropic degeneration and an appreciable infiltration of small lymphocytes and plasma cells. Occasional monocytes and eosinophils are to be seen. Russell bodies are numerous and prominent, while Mikulicz cells are less frequently noted. There is a dilatation of the vessels. Later in the disease, the picture is that of a chronic inflammatory process with plasma and lymphocytic cell infiltration. Gradually there is a

development of collagenous fibrous connective tissue, most pronounced around the vessels. The plasma and round cells disappear, and Mikulicz cells are more abundant. Only an occasional round cell or Russell body is seen. Finally, the vessels become thrombosed and their walls hyalinized, and the connective tissue degenerates and is replaced by scar tissue, with absence of vascular and lymphatic structures.

DIAGNOSIS

Clinical observation, as well as histologic and laboratory evidences, are all required in order for one to make a diagnosis of scleroma.

Clinically, the diagnosis of scleroma is to be considered with reference to the following factors: localization of the lesions to the respiratory tract and contiguous structures; absence of systemic involvement; absence of pain; hard, infiltrated tissues of an ivory-white color, with eventual cicatricial deformities; chronicity, with the disease slowly progressing for from ten to twenty years or more; the age of the patient, the condition rarely appearing after 40; and nationality, scleroma occurring mainly in foreign-born persons. Reyes [8] recently stated that he found anesthesia of the soft palate to be an important diagnostic sign in the earlier stages of the disease.

Laboratory aids in diagnosis include the complement fixation test, reactions being positive for approximately 92 per cent of scleromatous patients; the Forges-Elbert agglutination test; an intradermal test using an emulsion of killed K. rhinoscleromatis, and cultural isolation of K. rhinoscleromatis.

The identification histologically of the Mikulicz cell, the hyaline bodies of Russell and a plasma cell infiltration of the dermis allows for microscopic confirmation of the clinical diagnosis.

Scleroma, in its various stages progressing from the catarrhal phase to that of extensive sclerotic infiltrations, must be differentiated from atrophic rhinitis, rhinophyma, tuberculosis luposa (lupus vulgaris), Boeck's sarcoid, carcinoma, sarcoma, leprosy, syphilis, chronic glanders and verrucous leishmaniasis.

In the larynx, scleroma is subglottic and bilateral, which characteristics distinguish it from syphilis and tuberculosis.

PROGNOSIS

The prognosis in scleroma must be guarded at all times. If the diagnosis is made early, and if the disease is confined to the nose or the nasopharynx, adequate treatment may arrest the process completely. Tracheal and laryngeal scleroma offer a less favorable prognosis. Spontaneous termination through cicatrization seldom occurs. Death usually results from secondary intervening infection or asphyxia.

Szmurlo [17] expressed the opinion that chronic obstruction in the respiratory tract resulted in ultimate fatty degeneration of the cardiac muscle and that this fatty degeneration was the immediate cause of death in the majority of cases. Complications include syphilis, pulmonary tuberculosis, fungous infections and neoplasms.

PROPHYLAXIS

The familial transmission of scleroma has been a matter of discussion for many years. It evidently is not of common occurrence. No previous instance of possible familial transmission of the disease has been reported in the United States. Authorities are also divided in views as to the actual contagiousness of this disease. Poverty, malnutrition and lack of personal cleanliness are factors favoring its development. Burraud [18] in 1932 suggested that means to prevent scleroma should be studied by an international committee so that prophylactic measures might be instituted in all countries as a matter of national health.

TREATMENT

Myriad therapeutic agents and modalities have been promulgated in scleroma, with varying degrees of success, depending on the location and extent of the disease. Treatment with salicylates, mercurial preparations, iodides, arsenical compounds, antimony potassium tartrate (tartar emetic), local escharotics, autovaccines and foreign protein; autochemotherapy; malarial therapy; electrocoagulation, and curettage have all been used, without much success. Bougienage has frequently postponed tracheotomy. Surgical methods, such as laryngotracheotomy, have been frequently necessary and have often given beneficial results.

Irradiation has also proved to be of considerable value. Gottstein,[19] in 1902, first used roentgen rays for the treatment of scleroma, and in this country roentgen rays were first used by Pollitzer [20] and Ballin in 1906. Radium was first used in the United States by Guttman [21] in 1915. The dose of both roentgen rays and radium, as well as the technics employed, have varied considerably.

Azosulfamide, intramuscularly, also was advocated recently by Reyes.[8]

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17. Szmurlo, J.: Anatomicopathology of Scleroma, Arch. Otolaryng. **18**:393 (Sept.) 1933.

18. Burraud: International Legislation of Scleroma, Arch. Otolaryng. **18**:396 (Sept.) 1933.

19. Gottstein, cited by Weiss, J. A.: Scleroma (Rhinoscleroma): Histologic Changes Following Teleradium Therapy; Review of Scleroma in United States, Arch. Otolaryng. **30**:38 (July) 1939.

20. Pollitzer, S.: Laryngoscope **16**:963, 1906.

21. Guttman, J.: New York M. J. **102**:711, 1915.

Undoubtedly, the greatest therapeutic efficacy is to be achieved by a combination of methods, those used depending on the individual requirements in each case. These may include the discerning use of irradiation, surgical procedures and chemotherapy. In our case roentgen rays, radium, iodides and antimony potassium tartrate have arrested the

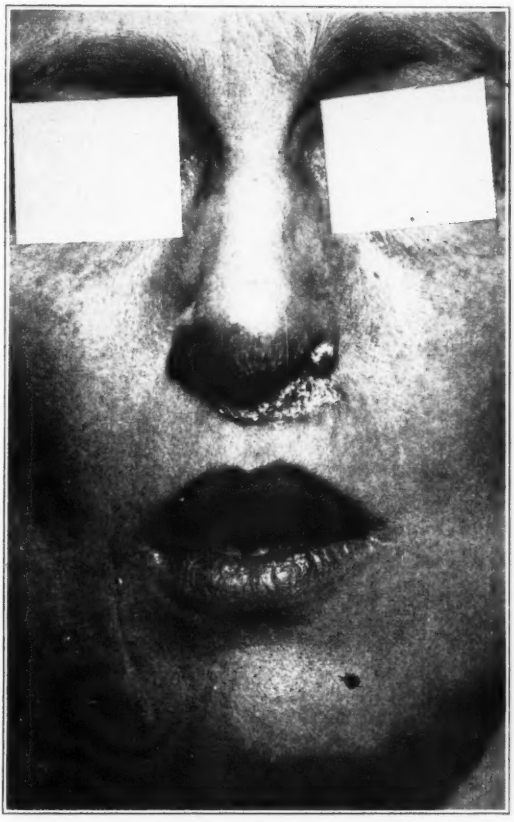

Fig. 1 (case 1).—Scleroma involving the nose, as seen in November 1941.

disease with apparent cure for a five year period. The most striking response was obtained by the use of roentgen rays and radium.

REPORT OF CASES

Case 1.—A. S. (fig. 1), a 41 year old white woman, was first seen by us on Nov. 17, 1941, complaining of swelling about the upper lip and nose, of eight years' duration. In addition, there was a persistent coryza and tenderness in the nose. Obstruction of the nasal passages had caused some respiratory difficulty.

The patient stated that she had first noticed a nodule on the skin at the junction of the lip and the septum of the nose in 1933. The lesion had enlarged slowly and had remained firm and hard. There had been some scaling but no exudation or pustulation. The lesion was painless. Concomitantly, there had developed rhinitis, as well as nasal tenderness resulting from the constant use of a handkerchief. The nose seemed to be constantly blocked, and during 1940 the nodule had been fulgurated, without benefit. The patient had received no other treatment. A diagnosis of scleroma was made. The patient was referred to an internist. A thorough physical examination, including a roentgenogram of the chest, revealed no other abnormal findings. The reaction to the Wassermann test was negative.

A specimen for histologic examination was taken from a nodule on the upper lip, close to the left side of the nose (fig. 2). The examination by Drs. D. Satenstein and W. Sachs revealed the presence of scleroma. They reported a cellular mass throughout the cutis, consisting of many plasma cells, some of which were hyalinized (Russell bodies). There were also many histiocytic-shaped cells, the cytoplasm of which had a granular foamy appearance (Mikulicz cells). The epidermis showed no important changes. The Gram stain revealed rodlike organisms.

Cultures of material taken from the nose and skin on March 14, 1942, grew no K. rhinoscleromatis. The patient was seen at the New York Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, service of Dr. Van Dyke, and subsequently was presented before the Section of Dermatology and Syphilology of the New York Academy of Medicine.

The patient received both roentgen radiation and radium therapy. A total dose of 1,750 of roentgen rays, filtered through 3 mm. of aluminum, was given to the sides of the nose and the upper lip. In addition 70 milligram hours of gamma radium with 0.5 mm. platinum-equivalent filtration was given to each nostril on three separate occasions. The patient improved rapidly. In 1943, after radiation therapy, the patient was given three injections of antimony potassium tartrate intravenously and subsequently twelve injections of potassium iodide intravenously at weekly intervals. Complete healing resulted, and the patient has been seen repeatedly until the date of writing, without any evidence of recurrence (fig. 3).

The family history in this case was most interesting. The parents had been born in Austria and had been in the United States for forty-five years. There were nine children. The patient had been born in Pennsylvania. At the age of six months, she had been taken to Austria for a visit of six months' duration.

Case 2.—A brother, M. S., was born in the United States and had never left the country. Lesions of the nose, pharynx and larynx had developed, beginning in 1919, when he was 18. He was seen at the Mayo Clinic on Feb. 18, 1927, and was presented at a meeting of the Minnesota Dermatological Society on April 6, 1927, by Drs. Paul O'Leary and Hamilton Montgomery.[11e] A diagnosis of scleroma was made on the basis of histopathologic observations of a specimen removed from the left ala. This was confirmed by cultural studies, in which K. rhinoscleromatis was demonstrated. Histologic sections revealed the bacilli in Mikulicz' cells and showed other changes characteristic of the disease.

In the discussion of this case at the time of presentation, Michelson stated that the disease, while relatively common in Central Europe, was rare in the United States. He further noted that the case was of unusual interest because of the fact that the patient, although he was of foreign parentage, had been born in this country and had never been out of the United States.

The patient received treatment with roentgen rays over a period of three months. A tracheotomy was performed because of laryngeal obstruction. The epiglottis was also amputated, and in September 1929 the stump of the epiglottis was removed. Despite all therapy, the patient died in 1930.

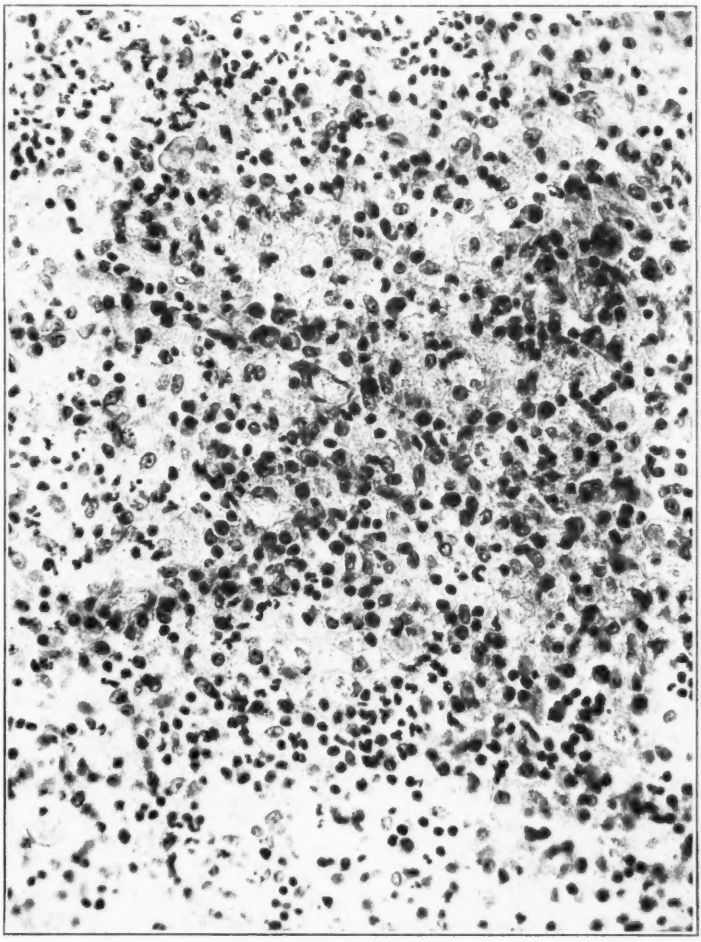

Fig. 2 (case 1).—Histologic section of nodule on upper lip, showing large, hyaline Russell bodies, as well as numerous Mikulicz cells, which have a foamy appearance. Numerous plasma cells are present.

CASE 3.—Another brother, J. S., enlisted in the Navy in 1926, at the age of 20. He served for three years without difficulty. In July 1929 he noticed a persistent sore throat, followed by hoarseness and protracted coryza. Breathing became

somewhat difficult. He stated that he felt as if there were an obstruction in his throat. He was transferred to a Navy hospital, where a submucous resection was done because of a deviated septum. Hoarseness, postnasal drip and partial aphonia persisted. Laryngeal examination in February 1930 showed a chronic inflammatory reaction of the laryngeal tissues. The ventricular bands were swollen. The vocal cords were irregular, with serrated edges. There was no evidence of paralysis. In the left fossa, near the anterior commissure, a small nodule was seen. Repeated examinations of sputum as well as roentgenograms of the chest revealed no evidence of tuberculosis. A diagnosis of chronic laryngitis was made at that time.

Sensations of suffocation then developed, and examination by L. H. Clerf[22] at the Bronchoscopic Clinic at the Jefferson Hospital during August 1930

Fig. 3 (case 1).—Photograph taken in April 1948, showing complete healing of the lesion of the nose and the upper lip.

revealed a pronounced "dyspnea due to obstructive edema of the larynx. It was impossible to arrive at any conclusions on the basis of mirror laryngoscopy because all the tissues about the upper orifice of the larynx were edematous and swollen. The changes suggested a tuberculous process, but at no time was a tuberculous lesion found. Repeated studies of secretions and also of tissue from the larynx were carried out, and all revealed no evidences of tuberculosis. Later it was possible to grow a fungus, a blastomycete, from the tissues removed through the tracheal stoma. It was necessary to do a tracheotomy for relief of dyspnea.

22. Clerf, L. H.: Personal communication to the author.

"All plans of therapy were attempted, including the use of iodides (ethyl iodide in particular) and everything else that has been tried in blastomycosis, but without benefit. The disease appeared to progress, extending down into the trachea and bronchi, and ultimately death ensued during 1943. At autopsy there was found a definite lesion, unquestionably blastomycotic, involving the larynx, trachea and bronchi, from which the fungus was recovered."

The patient had also been seen at the New York Post-Graduate Medical School and Hospital in March 1942, where examinations corroborated the findings of Dr. Clerf. Bacteriologic studies revealed no evidences of tuberculosis, blastomycosis or scleroma. No tissue could be taken for biopsy. Aside from an increased sedimentation rate (82 mm. in one hour) all other laboratory findings were well within normal limits.

COMMENT

We have not included the second brother, J. S., in table 1, since a diagnosis of scleroma was never definitely established. A question remains as to whether this blastomycetic infection was the primary etiologic agent or whether it was a secondary complication. We believe the latter situation to have existed, with both brothers having had scleroma; thus in this family there was a total of 3 children—all native-born Americans—with the disease.

SUMMARY AND CONCLUSIONS

A case of scleroma in a native-born American is presented. The patient gave a history of having had two brothers who were affected with this disease. It is our opinion that, although a blastomycetic infection was the cause of death for one of the brothers, the evidence submitted points to the impression that this infection was a secondary one. As has been previously noted, scleroma in itself is rarely the primary cause of death.

This is the first instance of multiple occurrence of scleroma in the same family to be reported in the United States.

The possibility of familial transmission and contagiousness of scleroma is still in doubt.

A summary of the 13 cases reported in native-born Americans is given.

The diagnosis of scleroma will undoubtedly be made more frequently in the future because of the actual numerical increase in the disease throughout the entire world and because of the physician's greater knowledge of and familiarity with the disease.

Drs. Paul O'Leary, Hamilton Montgomery and L. H. Clerf supplied much of the information concerning the reports of cases mentioned in this paper.

2 East Fifty-Fourth Street (Dr. Kline).

408 Home Savings and Loan Building (Dr. Brody).

MAMMALIAN TYROSINASE: MELANIN FORMATION BY ULTRAVIOLET IRRADIATION

THOMAS B. FITZPATRICK, M.D.
Fellow in Dermatology and Syphilology, Mayo Foundation
ROCHESTER, MINN.

A. BUNSEN LERNER, M.D., Ph.D.
CLEVELAND

EVAN CALKINS, M.D.
BALTIMORE
AND

WILLIAM H. SUMMERSON, Ph.D.
ARMY CHEMICAL CENTER, MD.

RAPER [1] and his associates, in a comprehensive study of the tyrosine-tyrosinase reaction, showed that the enzyme tyrosinase obtained from plant sources catalyzes the conversion of tyrosine to dopa (3,4-dihydroxyphenyl-l-alanine). Dopa is then oxidized, in the presence of the same enzyme, to a red indole derivative, which changes spontaneously to melanin.

Melanin formation in mammals has remained somewhat of an enigma, despite the demonstration by Bloch [2] of an intracellular oxidase which catalyzes the oxidation of dopa to melanin but is without apparent effect on tyrosine. The presence of dopa in mammalian tissue or fluids has never been demonstrated, and it has not been known how tyrosine is converted into dopa. Recently, however, the enzymatic formation of melanin from tyrosine has been conclusively demonstrated in several types of mammalian tissue, including beef ciliary bodies [3] and human,[4]

The work reflected in this study was carried out at the Army Chemical Center, Md.

1. Raper, H. S.: The Aerobic Oxidases, Physiol. Rev. **8**:245-282 (April) 1928.

2. Bloch, B.: Das Pigment, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol. 1, p. 434-541.

3. Calkins, E.; Lerner, A. B.; Fitzpatrick, T. B., and Summerson, W. H.: Mammalian Tyrosinase: Melanin Formation in Beef Ciliary Bodies, unpublished data.

4. Greenstein, J. P.; Werne, J.; Eschenbrenner, A. B., and Leuthardt, F. M.: Chemical Studies on Human Cancer: Cytochrome Oxidase, Cytochrome C, and Copper in Normal and Neoplastic Tissues, J. Nat. Cancer Inst. **5**:55-76 (Aug.) 1944.

horse [5] and mouse [6] melanomas. The enzyme has been shown to require copper for its activity [7] and to be firmly bound to cellular particulates.[6c] With the demonstration, therefore, of tyrosinase activity in various mammalian tissues, a scheme such as the one worked out by Raper and outlined in the first paragraph may also describe the mechanism of melanin formation in mammals. Recently one of us (T. B. F.) succeeded in demonstrating by histochemical methods the presence of tyrosinase in the melanoblasts of human epidermis.

Arnow [8] showed that ultraviolet irradiation of aqueous solutions of tyrosine over a period of four hours results in the formation of small amounts of dopa, as detected colorimetrically.[9] He postulated that when skin is exposed to ultraviolet radiation tyrosine in the skin is converted to dopa and the dopa oxidase in the melanoblasts then catalyzes the oxidation of dopa to melanin. Rothman [10] pointed out that the long period of exposure to ultraviolet radiation required for the conversion of significant amounts of tyrosine to dopa is not consistent with the phenomenon of tanning, which occurs after a shorter exposure. He demonstrated in vitro that addition of small amounts of ferrous salts catalyzes the conversion of tyrosine to dopa by ultraviolet irradiation, thereby reducing the necessary duration of exposure. He therefore suggested that ferrous salts or some unknown factors are present in the skin to catalyze this photochemical reaction. Recent results that we have obtained with tyrosinase from extracts of the Harding-Passey melanoma [6c] indicate the possibility of an alternate explanation for the relatively short time of exposure to ultraviolet radiation required in vivo for significant formation of pigment. We have found that, in the presence of trace amounts of dopa, tyrosine itself is rapidly and

5. Fitzpatrick, T. B.; Lerner, A. B.; Calkins, E., and Summerson, W. H.: The Occurrence of Tyrosinase in Horse and Fish Melanomas, Proc. Soc. Exper. Biol. & Med., to be published.

6. (*a*) Hogeboom, C. H., and Adams, M. H.: Mammalian Tyrosinase and Dopa Oxidase, J. Biol. Chem. **145**:273-279 (Sept.) 1942. (*b*) Greenstein, J. P., and Algire, G. H.: Comparative Oxidase Activity of Melanotic and Amelanotic Melanomas, J. Nat. Cancer Inst. **5**:35-38 (Aug.) 1944. (*c*) Lerner, A. B.; Fitzpatrick, T. B.; Calkins, E., and Summerson, W. H.: Mammalian Tyrosinase: Preparation and Properties, J. Biol. Chem. **178**:185-195 (March) 1949.

7. Lerner, A. B.; Fitzpatrick, T. B.; Calkins, E., and Summerson, W. H.: Mammalian Tyrosinase: On the Relationship of Copper to Enzymatic Activity, unpublished data.

8. Arnow, L. E.: The Formation of Dopa by the Exposure of Tyrosine Solutions to Ultraviolet Radiation, J. Biol. Chem. **120**:151-153 (Aug.) 1937.

9. Arnow, L. E.: Colorimetric Determination of the Components of 3,4-Dihydroxyphenylalanine-Tyrosine Mixtures, J. Biol. Chem. **118**:531-537 (April) 1937.

10. Rothman, S.: In Vitro Studies of Pigmentation: I. The Oxidation of Tyrosine by Ultraviolet Irradiation, J. Invest. Dermat. **5**:61-67 (April) 1942.

completely oxidized to form melanin by enzyme preparations which in the absence of the added dopa have little or no action on tyrosine, although they are highly active against dopa itself. It is therefore necessary to form only trace amounts of dopa in the presence of the enzyme and an adequate supply of tyrosine in order for formation of pigment to ensue at a rapid rate. Experimental evidence for the validity of this hypothesis, based on a study of the effect of ultraviolet irradiation on the ability of mammalian tyrosinase to oxidize tyrosine to melanin, forms the basis of this report.

EXPERIMENTAL METHODS

Tyrosinase was obtained from crude aqueous extracts of the Harding-Passey mouse melanoma.[6c] Solutions (0.0027 molar) of *l*-tyrosine were prepared with a 0.1 molar potassium phosphate buffer solution at p_H of 6.8.

Tyrosine and enzyme preparations buffered at p_H 6.8 were exposed separately to unfiltered ultraviolet radiation from a carbon arc source [11] at 30 inches (about 76 cm.) for thirty minutes at room temperature (minimal erythema dose, 1 minute). A decrease of volume as a result of evaporation was compensated for by addition of enough water to restore the original volume.

Manometric measurements of the oxygen uptake in the Warburg apparatus were used to follow the course of the enzymatic oxidation reaction, which was carried out at 38 C. in a 0.1 molar potassium phosphate buffer solution at p_H 6.8. Experimental conditions are given in figure 1.

RESULTS

The action of the unirradiated enzyme on the irradiated and the unirradiated tyrosine was studied first. As is shown in figure 1, oxygen uptake began sooner in the reaction mixture containing irradiated tyrosine than in the mixture containing the unexposed substrate, a fact which indicates an increased rate of melanin formation in the sample with irradiated tyrosine. The formation of melanin was followed by means of comparison of samples of the reaction mixtures taken at various intervals during the reaction. Photometric comparisons of these samples in a photoelectric colorimeter were in agreement with the manometric findings; that is, darkening appeared earlier in the mixture containing the irradiated tyrosine. Analysis of the irradiated tyrosine solutions by Arnow's colorimetric method indicated the presence of a dihydroxyphenyl compound.

It can be seen from figure 1 that the exposed substrate had less total oxygen uptake than did the unexposed tyrosine solution, this fact indicating a reduction in the amount of tyrosine after irradiation.

When the irradiated enzyme was combined with the unirradiated tyrosine, the rate of oxygen uptake was less than that with the control,

11. Model A-2 carbon arc lamp, National Carbon Company, Inc., with National® therapeutic high intensity carbon rods.

a fact which suggests a partial inactivation of the enzyme by the radiant energy. The foregoing experiments were repeated on four occasions with substantially identical results.

COMMENT

The experiments presented demonstrate that irradiation of tyrosine solutions produces a factor which increases the rate of melanin formation in the tyrosine-tyrosinase reaction. The following points suggest that dopa is the accelerating factor:

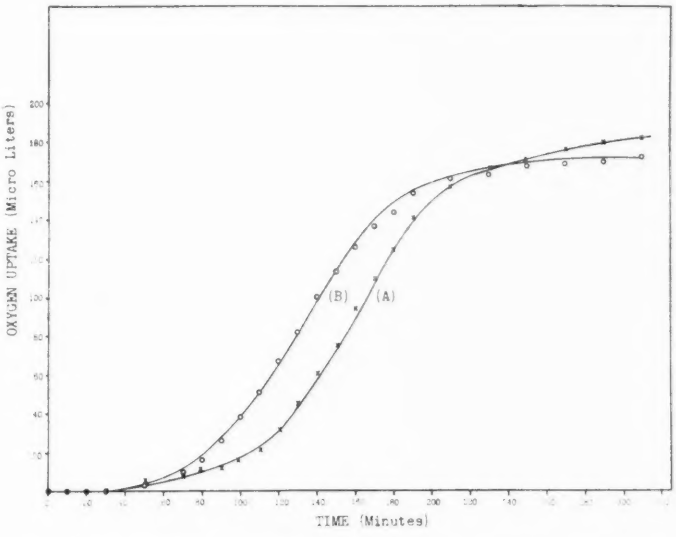

Fig. 1.—The enzymatic oxidation of tyrosine and irradiated tyrosine by an extract of the mouse melanoma at p_H 6.8 and 38 C. *A* represents oxidation with 0.25 cc. of extract plus a solution of 0.5 mg. tyrosine in 2.75 cc. of 0.1 molar potassium phosphate buffer solution, and *B*, with 0.25 cc. of extract plus an irradiated solution of 0.5 mg. tyrosine in 2.75 cc. of 0.1 molar potassium phosphate buffer solution.

1. The findings indicate, in confirmation of the results of Arnow and of Rothman and associates,[12] that a dihydroxyphenyl compound is formed in the irradiated solutions.

12. (*a*) Rothman, S.; Krysa, H. F., and Smiljanic, A. M.: Inhibitory Action of Human Epidermis on Melanin Formation, Proc. Soc. Exper. Biol. & Med. **62**:208-209 (June) 1946. (*b*) Rothman, S., and Flesch, P.: Personal communication to the authors.

2. In previous experiments [6c] we found that trace amounts of dopa accelerate the enzymatic formation of melanin from tyrosine in a manner similar to that observed in the experiments reported here.

3. Evans and Raper [13] were able to isolate crystalline dopa after oxidation of tyrosine with hydrogen peroxide. It is generally accepted that irradiation of water in the presence of dissolved oxygen results in the formation of hydrogen peroxide. Ultraviolet irradiation and hydrogen peroxide may oxidize compounds through similar mechanisms.

It is therefore probable that irradiation of mammalian skin results in the formation of trace amounts of dopa from tyrosine; dopa, in

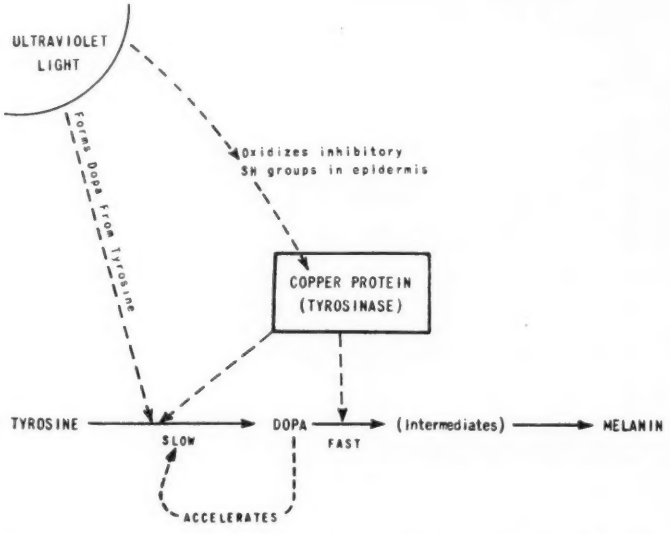

Fig. 2.—Formation of melanin from tyrosine by ultraviolet irradiation.

addition to being oxidized to melanin, also accelerates the enzymatic oxidation of tyrosine to melanin.

The recent experiments of Rothman and associates [12a] with aqueous extracts of human epidermis suggested a further, and perhaps equally important, factor in the formation of melanin by ultraviolet light. They were able to demonstrate that in the presence of aqueous extracts of human epidermis there was inhibition of the enzymatic oxidation of tyrosine to melanin by plant tyrosinase. This inhibition was abolished by compounds which combine with -SH groups and by ultraviolet

13. Evans, W. C., and Raper, H. S.: The Accumulation of 1-3:4-Dihydroxyphenylalanine in the Trosinase-Tyrosine Reaction, Biochem. J. **31**:2162-2170, 1937.

irradiation of the extracts.[12b] These experiments indicated that the inhibitory effect of human epidermis is due to the presence of sulfhydryl groups, which probably bind the copper required for enzymatic activity, and that ultraviolet irradiation may play a dual role in the formation of cutaneous pigment.

The interrelations of the various factors, discussed in previous paragraphs, which are responsible for the formation of melanin from tyrosine by ultraviolet irradiation are schematically illustrated in figure 2.

SUMMARY

Ultraviolet irradiation of tyrosine solutions results in the formation of a factor, probably dopa (3,4-dihydroxyphenyl-l-alanine), which catalyzes the oxidation of tyrosine to melanin by mammalian tyrosinase.

Ultraviolet irradiation of tyrosinase results in a slight inactivation of the enzyme, as indicated by a decreased rate of oxygen uptake of the tyrosine-tyrosinase reaction mixture.

A new hypothesis is advanced for the photochemical reaction underlying the formation of melanin in the skin by ultraviolet irradiation.

Mayo Foundation (Dr. Fitzpatrick).

Department of Biochemistry, Western Reserve University School of Medicine (Dr. Lerner).

Department of Internal Medicine, Johns Hopkins Hospital (Dr. Calkins).

Biochemistry Section, Medical Division (Dr. Summerson).

MASSIVE METASTASIZING MENINGIOMA INVOLVING THE SCALP

CARL W. LAYMON, M.D.
MINNEAPOLIS
AND
FREDERIC T. BECKER, M.D.
DULUTH, MINN.

MENINGIOMAS are tumors of the meninges of the brain or spinal cord. There are several types, distinction of which depends primarily on the morphologic features and architecture of the tumor cells. Most writers have expressed the belief that meningiomas almost never metastasize. In this paper is reported a most unusual example of a meningioma which eroded the skull, invaded the scalp and metastasized to the cervical nodes. Although many sources were carefully studied, we were unable to find any case in the literature similar to this one, which is unique in our experience.

REPORT OF A CASE

V. T., a white man aged 72, acquired a swelling in the right frontal portion of his scalp in 1941. The tumor gradually grew until it attained a size approximately that of the head by April 1947. At that time the patient noticed weakness of the left arm and leg, and early in May 1947 he fell unconscious. He was admitted to the hospital on July 1 and stated that he had experienced periods of unconsciousness for several months. His friends said that there had been a loss of mental faculties for five years.

There was nothing important in the past history. In 1910 the patient had been injured in a mine accident and had suffered a laceration of the scalp, but there had been no loss of consciousness and the injury had healed uneventfully.

Examination.—There was a soft, compressible, bluish red tumor about the size of two grapefruits in the right frontal and parietal regions of the scalp. Although the general consistency was soft, a few areas were firm. There were numerous large blood vessels coursing over the surface, and the hair was extremely sparse over the growth. On auscultation with a stethoscope there was noted a definite bruit coincidental with the heart beat. The left pupil was slightly larger than the right, although both pupils reacted to light and in

Read at the Sixty-Eighth Annual Meeting of the American Dermatological Association, Inc., San Diego, Calif., April 27, 1948.

From the Division of Dermatology, University of Minnesota, E. Michelson, M.D., director, the Department of Dermatology, Minneapolis General Hospital, Carl W. Laymon, M.D., Director, and the Duluth Clinic.

accommodation. There were several enlarged posterior cervical nodes, one of which was about the size of an egg. The blood pressure was 140 systolic and 70 diastolic.

Laboratory Findings.—Urinalysis gave completely normal results; the hemoglobin content was 11.5 Gm. per hundred cubic centimeters, the red blood cell count 4,500,200, and the white blood cell count 10,200, with a normal differential count. Serologic tests for syphilis gave negative reactions. A roentgenogram of the skull showed destruction of the inner and outer tables of the right frontal and parietal bones, and similar examination of the chest showed no areas of infiltration or consolidation. The heart was slightly enlarged, and the aorta was calcareous and more tortuous than normal. Intravenous pyelograms showed a normal condition.

Course.—While the patient was in the hospital there was gradual improvement in the weakness in the left arm and the left leg. At the time of the patient's

Fig. 1.—Meningioma which eroded the skull and massively invaded the scalp.

discharge, in August 1947, there was residual weakness in both extremities. During the period of hospitalization the surgeons were reluctant to remove a portion of the tumor for biopsy because of the possibility that the patient might die of hemorrhage. One of the enlarged cervical lymph nodes was removed and studied histologically. The sections were examined by several pathologists: Drs. E. T. Bell, A. C. Broders, Hamilton Montgomery, J. S. McCartney and R. Hebbel. All agreed that the histologic picture was consistent with a diagnosis of malignant, noncornifying epithelioma. Montgomery and Broders judged that it was grade 3 on Broders' classification.

The patient died on Jan. 10, 1948, and permission for necropsy was obtained. The tumor of the scalp measured 19 cm. in its transverse diameter, 12.5 cm. anteroposteriorly and 11 cm. in height. The lesion was formed by two round masses, which were partly fused. The spherical mass over the right half of

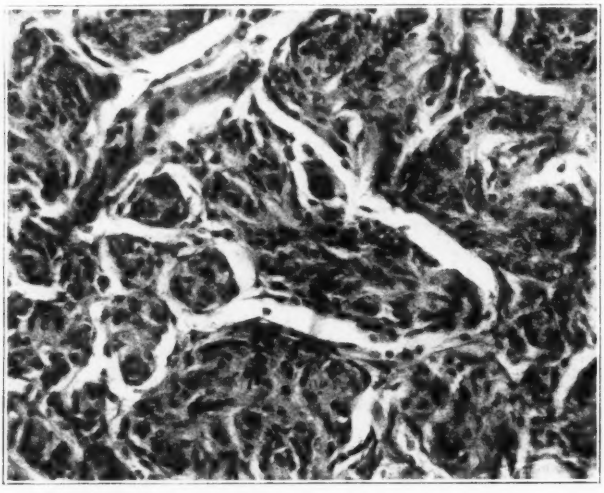

Fig. 2.—Histologic section from the scalp, showing cellular units in whorled arrangement.

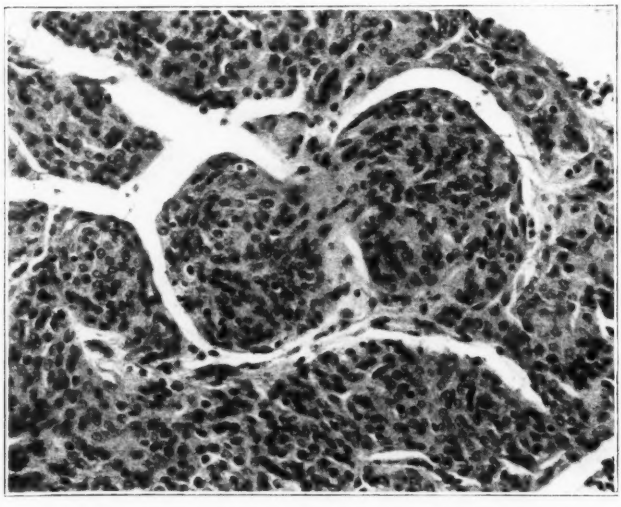

Fig. 3.—Histologic section from a metastasis in a cervical node, showing the same concentric arrangement of cells as in the primary tumor.

the head was not as high as that over the left half. The skin overlying the tumor was adherent to the underlying structure in various places, and several large, tortuous veins coursed over the surface. On the cut surface the tumor tissue was grayish white and there were several necrotic areas. The mass which infiltrated the scalp came from within the cranium through an irregular, roughly circular defect of the skull, 9 cm. in diameter. The pathologist stated that it was impossible to be certain concerning the point of origin of the tumor (dura, arachnoid or pia mater). The intracranial mass was situated over the right cerebral hemisphere. The tumor, including that part which had infiltrated the scalp, weighed 2,300 Gm. The mass within the cranium was continuous with that which had infiltrated the scalp, and the brain tissue beneath the tumor, especially that of the right parietal lobe, was depressed. Except for the aforementioned metastases in the cervical nodes, there were none throughout the entire body.

Histologic sections of the primary tumor were examined by Drs. Hamilton Montgomery, A. C. Broders and James Kernohan, who made an unequivocal diagnosis of meningioma of the meningothelial type. Broders stated that meningiomas of this type can simulate squamous cell epithelioma.

COMMENT

The diagnosis of rare tumors of the scalp constitutes an interesting but, unfortunately, confusing problem. The case reported here was presented for diagnosis by Dr. F. T. Becker at a meeting of the Minnesota Dermatologic Society, in Duluth, during the summer of 1947. It was the consensus that the most likely clinical diagnosis was hemangioendothelioma.

Sweitzer and Winer,[1] in 1936, defined hemangioendothelioma as a tumor possessing low grade malignancy, a characteristic clinical appearance and a precise histologic structure. Hemangioendothelioma is composed essentially of blood spaces and vessels in different stages of development. These authors maintained that true endothelioma of the skin does not exist, since an endothelioma must arise from endothelium-lined structures, such as blood or lymph vessels; therefore, the so-called endothelioma of the external surface is either a hemangioendothelioma or a lymphangioendothelioma. They also called attention to the fact that many tumors diagnosed as endothelioma are in reality epithelioma or sarcoma.

Hemangioendothelioma occurs on almost any part of the body and may vary in size from that of a pea to that of an orange. The lesion is dark red and moderately soft and may or may not be surrounded by satellites. One of the patients of Sweitzer and Winer presented a soft, reddish tumor, 10 cm. in diameter, in the right iliac region. This type of neoplasm may ulcerate and bleed profusely. There is a tendency toward infiltration, and the lesion may attach itself to underlying tissue

1. Sweitzer, S. E., and Winer, L. H.: Hemangio-Endothelioma, Arch. Dermat. & Syph. **34**:997 (Dec.) 1936.

and bone or to overlying skin. Tenderness is not a prominent feature. The degree of local malignant change may be slight, or there may be a decided tendency toward penetration. The ability to metastasize is low, and, according to Sweitzer and Winer, it is doubtful whether subsequent growths may be regarded as metastases or as lesions of multicentric origin.

The histologic structure of hemangioendothelioma consists of three related zones, each gradually fusing into the other without any definite line of demarcation. In the center of the tumor are mature structures, and toward the periphery the vessels gradually become immature. The central core consists of capillaries filled with blood, and surrounding this are solid cords or strands or cells, which are attempting to form lumens. Irregular masses of cells showing no features of differentiation form the outer border of the neoplasm. The individual cells are large and exhibit a clear cytoplasm and a nucleus which is relatively small. The histologic features of the tumor in our case immediately ruled out a diagnosis of hemangioendothelioma. There was no conglomerated mass of capillaries and spaces but a diffuse deposit of infiltrating cells.

In almost all cases of neoplasms of the scalp the question of pure turban tumor (cylindroma, benign epithelioma of the scalp or nevus epitheliomatocylindromatosus) arises. Cylindroma may occur as single or as multiple tumors of the scalp or the glabrous skin. The lesions are round, bluish or reddish and firm and as a rule do not ulcerate. They rarely appear after the age of 40 but if left untreated may continue to grow slowly to a large size. Women are affected more frequently than are men, and there is a definite hereditary factor, several members of one family often being affected. Binkley,[2] who thoroughly surveyed the subject in 1937, stated that malignant tumors of the scalp, unless they can be demonstrated to arise from the benign basal cells of atypical cylindroma, should be excluded from this classification.

The histologic picture of cylindroma is striking and shows an arrangement of basal cells in round, oval or elongated nests, packed closely, so that the tumor is in almost solid lobules. The latter are surrounded by hyalin-like connective tissue membranes, and there may also be intracellular hyaline changes. The histologic features in our case completely ruled out a diagnosis of cylindroma.

In 1937 Tauber, Goldman and Barrett [3] reported a peculiar tumor of the scalp of six years' duration in a middle-aged Negro. It began as a few discrete nodules and later became invasive and metastasized. On admission to the hospital the patient presented a diffuse enlargement

2. Binkley, G. W.: Naevus Epitheliomato-Cylindromatosus, Arch. Dermat. & Syph. **37**:289 (Feb.) 1938.

3. Tauber, E. B.; Goldman, L., and Barrett, C.: Mesenchymoma: A New Type of Turban Tumor, Arch. Dermat. & Syph. **37**:444 (March) 1938.

of the scalp, the greatest circumference being 75 cm. In the occipital area there were two ulcers, 4 cm. in diameter. There were small, discrete submental and postauricular nodes. The tumor grew; the surface of the skin became dark brown; the mass became less firm, and fistulous tracts appeared through the scalp. At necropsy metastases were found in the ribs and the kidneys. Because the authors were unable definitely to classify the tumor and because the cells were young and undifferentiated, the term "mesenchymoma" was applied. Discussers of the paper agreed that the tumor did not fit in with the cylindromas but that it might possibly be a highly malignant epithelioma (H. Montgomery), a form of lymphoblastoma or possibly mycosis fungoides (D. Satenstein and F. Weidman).

In the case of "mesenchymoma" reported by Tauber, Goldman and Barrett, the histologic observations were reported as follows: There was invasion of the skin and subcutaneous tissues by tumor cells which were large and undifferentiated, had oval or round nuclei rich in chromatin and frequently had nucleoli. The cells contained pale cytoplasm and when stained by the Van Gieson method showed an intertwining network of short cytoplasmic processes. No relation of these cellular masses to blood or lymph vessels or other structures could be seen. The metastatic lesions presented the same histologic picture as did the primary tumor. Tauber, Goldman and Barrett stated in their article that their case had been diagnosed by some dermatopathologists as epithelioma and by others as sarcoma or endothelioma. Apparently, because of this confusion, these authors believed that a new classification was needed for this tumor. It seems to us, however, that the case in question probably fitted into one of the fixed classes of tumors, most likely malignant epithelioma, an opinion which was stated by Montgomery in discussion of the case.

Meningioma is a relatively common intracranial tumor. It is usually extracerebral, although intraventricular meningiomas have been reported.[4] In the series of Cushing and Eisenhardt [5] there was 1 case of meningioma to every 4 cases of glioma. Meningioma has also been called dural endothelioma and dural fibroma. Boyd [6] objected to the term dural endothelioma because he thought that the growth did not arise from

4. Abbott, K. H., and Courville, C. B.: Intraventricular Meningiomas: Review of the Literature and Report of Two Cases, Bull. Los Angeles Neurol. Soc. **7**:12, 1942.

5. Cushing, H., and Eisenhardt, L.: Meningiomas: Their Classification, Regional Behavior, Life History, and Surgical End Results, Springfield, Ill., Charles C Thomas, Publisher, 1938.

6. Boyd, W.: Surgical Pathology, ed. 6, Philadelphia, W. B. Saunders Company, 1947.

the dura and that it was not an endothelioma. He stated he believed that the site of origin of meningioma is the arachnoid mater, in those groups of mesothelial cells which are observed in connection with or close to the arachnoid villi. Bell,[7] however, stated that meningiomas grow from the dura mater of the brain or of the spinal cord. Ewing [8] mentioned that the tumors first appear as flat elevations on the inner side of the dura, which growths slowly enlarge with corresponding displacement or atrophy of brain substance. He stated the belief that the chief seats are the dura over the convexity in the falx and tentorium and along the basal vessels and that meningiomas may develop over the medulla and down to the cauda. Ewing stated that the endothelial features of meningioma are so obvious that the tumor was the first to receive the designation of endothelioma (Golgi, 1869). The origin of the cells has been referred chiefly to the endothelium of perivascular lymph spaces and to the perithelium of proliferating vessels, although these structures have been regarded as derivatives of the lining cells of the dura. Ewing stated the belief that probably most or all of the endothelial tumors of the dura are derived from groups of endothelial cells, which he found, in a large proportion of adults, lying in the meshes of the pia, near small blood vessels, and especially in connection with pacchionian granulations.

Cushing preferred to call these tumors meningioma because they seemed to arise from a specialized cell, the meningocyte, which he found exerted a specific physiologic function. Ewing expressed the opinion, however, that since the meningocyte differentiates toward the fibroblast, laying down intercellular material in tumors or producing cells virtually identical with vascular endothelium or, again, exhibiting angioblastic qualities, meningioma seemed to fall within the class of endotheloma and its variants.

Meningiomas present a wide variation in structure. Secondary changes, such as fibrosis, hyalinization and calcification, are frequent. In fact, Mallory [9] and, later, Penfield [10] tried to prove that the typical cell in these tumors is a fibroblast and that therefore the growths should be called arachnoid fibroblastomas. French pathologists have spoken of neuroepithelial and gliomatous types of meningeal tumors. Bailey

7. Bell, E. T.: A Text-Book of Pathology, ed. 4, Philadelphia, Lea & Febiger, 1941.

8. Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, ed. 4, Philadelphia, W. B. Saunders Company, 1940.

9. Mallory, F. B.: The Type Cell of the So-Called Dural Endothelioma, J. M. Research **41**:349, 1920.

10. Penfield, W.: The Encapsulated Tumors of the Nervous System; Meningeal Fibroblastomata, Perineurial Fibroblastomata and Neurofibromata of von Recklinghausen, Surg., Gynec. & Obst. **45**:178, 1927.

and Bucy [11] went even further and divided meningeal tumors into nine types: mesenchymal, angioblastic, meningealtheliomatous, osteoblastic, psammomatous, fibroblastic, melanoblastic, sarcomatous and lipomatous. Cushing also listed nine major types, with subvariations of each.

Courville and Abbott,[12] in a survey of the different types of meningiomas based on a series of 99 cases, came to the following conclusions:

1. There are five unequivocal types of circumscribed meningeal tumors:
   (*a*) Syncytial (the so-called meningothelial type).
   (*b*) Fibrous (fibroblastic).
   (*c*) Transitional (with combined characteristics of the above two types).
   (*d*) Angioblastic (which forms a constellation all its own).
   (*e*) Malignant or sarcomatous.

(The authors mentioned that other types of meningioma [mesenchymatous, chondromatous] might be just as clear cut in their identity but that they could not certify them on the basis of their own experience.)

2. Classification into these five types is based primarily on the morphologic features and the architecture of the tumor cells, secondary importance being placed on the formation of reticulin and collagen.

3. In spite of the common occurrence of true whorl formation, it is not advisable to create a special type of meningioma on the basis of this feature alone, since this structural detail occurs in every other type of tumor, not excluding angioblastic. The term "psammomatous meningioma" is misleading, since psammoma bodies are observed in many varieties of meningiomas. These bodies are regressive in character and play no recognized part in the neoplastic process.

4. It is questionable whether or not a separate group of osteoblastic meningiomas should be established. The presence of bone in meningiomas is the result of a degenerative change or a reaction of the bone of the skull and not a neobiologic activity of the tumor cells.

5. Lipomas were likewise not included in the group because these tumors are not meningiomas whose cells produce fat but are true lipomas, similar to those found elsewhere in the body.

6. Diffuse sarcomatous and melanoblastomatous tumors have likewise been omitted because of their different appearance, behavior and clinical manifestations. Their inclusion only confuses the issue.

7. The creation of subtypes, which make any classification impractical for routine use, should be avoided because variations in morphologic character, constituent cells and architectural arrangement are almost endless.

From this summary it can easily be seen that there is no general agreement concerning either the site of origin of meningiomas or the exact type of cell which makes up the tumor.

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11. Bailey, P., and Bucy, P. C.: The Origin and Nature of Meningeal Tumors, Am. J. Cancer **15**:15, 1931.

12. Courville, C. B., and Abbott, K. H.: On the Classification of Meningiomas, Bull. Los Angeles Neurol. Soc. **6**:21, 1941.

One can realize, considering the large number of different types of meningioma, that the histologic picture is subject to wide variation. The tumor tissue is composed of systems of cells concentrically arranged about a central lumen, closed or patent, which represents a rudimentary vessel. These units may be small, numerous and sharply defined or large and ill defined. Considerable areas may be composed of diffuse cells without concentric arrangement, or the masses may be plexiform and convoluted. The individual cells are polyhedral or of elongated spindle form, and in some extremely cellular forms the cell borders are less distinct and the nuclei hyperchromatic. Whorling of the cells constitutes one of the most characteristic histologic features. In cases in which no whorls are seen, the structure may simulate hard fibroma or fibrosarcoma. In these cases there are numerous collagenous fibers. In other cases there are few or no collagenous fibers. In other meningiomas the whorls are replaced by thick, homogeneous, hyaline bands, often with a small deposit of calcium salts in the center.

Cutaneous psammomatous meningiomas have been referred to by Dietel,[13] Gans,[14] Eller,[15] Ormsby and Montgomery [16] and Andrews.[17] The first instance of psammoma of the skin was reported by Winkler. His case was characterized by firm nodules located in the deeper layers of the cutis and the subcutis situated along the vertebral column. The tumors presented a varying clinical appearance. Some resembled soft moles, while others showed peculiar projections which resembled mamillae. The skin overlying some of the lesions was atrophic and grayish red. After Winkler's first case, others were reported by Kothe, Lennhoff, Naegeli and Hofmann in Jadassohn's clinic.[18] In these cases the tumors were located in the occipital region and the overlying skin was devoid of hair. No subjective symptoms were reported. Psammomas of the skin have been referred to as endothelial new growths identical with psammomas of the meninges, both histologically and pathogenetically. Histologically the lesions were located in the cutis and subcutis and consisted of strands of cells with large vesicular nuclei. Calcium deposits, thought to be derived from calcified connective tissue fibers, were located between the cellular strands. Nerve fibers were also

13. Dietel, F., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1932, vol. 12, pt. 2.

14. Gans, O.: Histologie der Hautkrankheiten, Berlin, Julius Springer, 1928, vol. 2.

15. Eller, J. J.: Tumors of the Skin: Benign and Malignant, Philadelphia, Lea & Febiger, 1939.

16. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 7, Philadelphia, Lea & Febiger, 1948.

17. Andrews, G. C.: Diseases of the Skin for Practitioners and Students, ed. 3, Philadelphia, W. B. Saunders Company, 1946.

18. Cited by Dietel.[13]

noted, surrounded by connective tissue which closely resembled the tissue of the dura mater. Cutaneous psammomas have been regarded as developmental disturbances and have been observed in the same regions as have meningoceles and encephaloceles. This observation may indicate that, genetically, psammoma may be traced to a displacement of meningeal germ cells at the site of embryonal fissuring. In the few cases of psammoma localized to the skin, diagnosis has been possible only by means of histologic examination. The tumors were all benign and were best treated by means of surgical excision.

A meningioma is usually firm, in comparison with a glioma. The tumors may be single and as large as a hen's egg or multiple and of miliary dimensions. They may grow into the brain to such an extent that they appear to be completely surrounded by cerebral substance and show no obvious connection with the arachnoid, but they never really perforate the pia. They are usually well encapsulated. Local changes in the skull overlying the tumors are common and are of two types: local erosion and bony thickening. Erosion, especially perforation of the skull, is rare, while bony thickening is much commoner. Cushing reported cranial hyperostosis in 25 per cent of 80 cases of meningioma.

The course of the tumor is slowly progressive. Symptoms due to pressure are usually late in appearance, and many growths are first discovered at autopsy. Some authorities state flatly that meningiomas never metastasize, a view which obviously is not unanimous. Ewing cited a case in which there were metastatic nodules in the lung and another in which there was a metastatic lesion in the bladder but stated that metastases were extremely rare. Cushing mentioned that meningiomas, even those of sarcomatous type, appear never to produce metastasis either within or without the craniospinal chamber. He observed, however, metastasis to the lungs in 1 of his cases. As far as we can find, there has never previously been reported a case of meningioma which has perforated the skull, massively invaded the scalp and metastasized to the cervical nodes.

SUMMARY

A case of meningioma which eroded the skull, herniated into the scalp and metastasized to the cervical nodes is reported.

Meningiomas are extracerebral intracranial tumors which almost never metastasize. The site of origin and the primary type of cell constituting the tumor are still debatable.

A few isolated cases of cutaneous psammoma have been reported. These apparently have sprung from embryonal meningeal rests.

345 Medical Arts Building.
Duluth, Clinic.

BALANITIS XEROTICA OBLITERANS

Report of a Case

DAVID G. WELTON, M.D.
AND
PRESTON NOWLIN, M.D.
CHARLOTTE, N. C.

BALANITIS xerotica obliterans, originally described by Stühmer [1] in 1928, was defined by Laymon and Freeman [2] as "a chronic, progressive, atrophic, sclerosing process of the glans and prepuce leading to urethral stenosis." Madden's report [3] in 1935 of 3 patients with this condition was the first to appear in the American literature. From 1941 until early 1947 at least 28 more cases were described in our literature [4] (table). It is probable that the same condition had previously been described under the names of kraurosis penis,[4b] balanosclerosis [5] and lichen sclerosus et atrophicus.[6] Freeman and Laymon summarized these reports in a comprehensive review of the literature in 1941.[4b] These authors demonstrated that this disease may occur at any age between 22 and 67, that it is not necessarily associated with circumcision or any other operative procedure, that it may be accompanied with lesions on the body characteristic of lichen sclerosus et atrophicus and that the histologic features of balanitis xerotica obliterans are identical with those of

1. Stühmer, A.: Balanitis xerotica obliterans (post-operationem) und ihre Beziehungen zur "Kraurosis glandis et praeputii penis," Arch. f. Dermat. u. Syph. **156**:613, 1928.

2. Laymon, C. W., and Freeman, C.: Relationship of Balanitis Xerotica Obliterans to Lichen Sclerosus et Atrophicus, Arch. Dermat. & Syph. **49**:57 (Jan.) 1944.

3. Madden, J. F.: The Balanitides, J. A. M. A. **105**:420 (Aug. 10) 1935.

4. (*a*) Laymon and Freeman.[2] (*b*) Freeman, C., and Laymon, C. W.: Balanitis Xerotica Obliterans, Arch. Dermat. & Syph. **44**:547 (Oct.) 1941. (*c*) Foerster, H. R., in discussion on Freeman and Laymon.[4b] (*d*) Novy, F. G., Jr.: Balanitis Xerotica Obliterans, Arch. Dermat. & Syph. **43**:397 (Feb.) 1941. (*e*) Leifer, W.: Balanitis Xerotica Obliterans, ibid. **49**:118 (Feb.) 1944. (*f*) Johnson, H. M.: Balanitis Xerotica Obliterans, ibid. **49**:299 (April) 1944. (*g*) Franks, A. G.: Balanitis Xerotica Obliterans, J. Urol. **56**:243 (Aug.) 1946. (*h*) Frishwasser, E. J., and Finkle, T. H.: Balanitis Xerotica Obliterans: Report of a Case, ibid. **57**:359 (Feb.) 1947.

5. Schildkraut, J. M.: Balanosclerosis with Beginning Epithelioma, Arch. Dermat. & Syph. **49**:205 (March) 1944.

6. Nicholson, M. A., and Becker, F. T.: Lichen Planus Sclerosus et Atrophicus, Arch. Dermat. & Syph. **43**:430 (Feb.) 1941.

lichen sclerosus et atrophicus. Meatal stenosis occurred in all the patients in their series. Other conditions frequently noted in these patients were a constricting band of the prepuce, sclerosis of the frenum

Observations in Cases of Balanitis Xerotica Obliterans in the American Literature, 1935 to 1947

Age of Patient	Duration of Lesions	Previous Operation	Meatal Stenosis	Previous Infection	Lesions Elsewhere	Biopsy	Author
23	1 yr.	None	Present	None	.....	Yes	Madden[3]
22	3 yr.	None	Absent	Trauma 3 mo. previously	.....	....	
24	5 yr.	None	Present	Gonorrhea	.....	....	
54	1 yr.	23 yr. previously	Present	Tight foreskin since childhood	Vitiligo	No	Novy[4d]
22-65 (18 cases)	.....	None	Present in all	Balanoposthitis (1 case)	Lichen sclerosus et atrophicus (in some cases)	Yes (in some cases)	Freeman and Laymon[4b]
62	6 yr.+	Dorsal slit 18 mo. previously	Present	Yes	.....	Yes	Foerster[4c]
25	4 yr.	None	Present	.....	Lichen sclerosus et atrophicus on body	....	Laymon and Freeman[2]
55	.....	None	Present	.....	Lichen sclerosus et atrophicus on body	No	
37	1 yr.	None	Present	.....	Lichen sclerosus et atrophicus on body	No	
67	1 yr.	None	Present	.....	Lichen sclerosus et atrophicus on shaft	Yes	
22	1 yr.	None	Present	Urethral discharge	None	Yes	Leifer[4e]
46	.....	4 yr.	Present	.....	.....	....	Johnson[4f]
21	5 yr.	Circumcision	Present	.....	None	Yes	Franks[4g]
29	7 mo.	None	Present	None	.....	Yes	Frishwasser and Finkle[4h]
38	2 yr.	None	Absent	None	None	Yes	Welton and Nowlin

Total.....32 cases

and recurring erosions and fissures of the glans. All the patients whose cases are listed in the accompanying table were white men; biopsies were reported in about one-half the cases.

In spite of the fact that meatal involvement was a constant observation in the reported cases, none of the patients was subjected to a thorough

urologic examination.[7] We wish therefore to report our observations on a patient who presented the characteristic clinical and histologic features of balanitis xerotica obliterans, including invasion of the ventral half of the meatus, which did not result in stenosis because the dorsal (uninvolved) half of the meatus exhibited normal elasticity in a compensating manner. Careful endoscopy of the anterior portion of the urethra showed no evidence of a sclerosing process proximal to the meatus. In order to determine the presence or absence of any associated pathologic condition of the genitourinary tract, we made a complete urologic study.

Fig. 1.—Triangular shape and irregular border of the lesion on the glans. The meatus is entirely surrounded by the atrophic skin.

REPORT OF CASE

B. F. P., a married white man aged 38, was first seen by us on Sept. 16, 1946, complaining of pain on sexual intercourse. He stated that about two years prior to this date he had noticed an eruption on the inner surface of the prepuce. Shortly afterward he had noted "white spots" on the glans penis; these had slowly increased in size since that time. Two months after the onset he had consulted his family physician, who had excised a portion of his frenum on two occasions, with no apparent benefit, although the wounds had healed promptly after each operation. Several ointments had been used on the penile eruption, without improve-

7. Franks's report [4g] did include determinations of urea nitrogen, chlorides and sugar in the blood and of the basal metabolic rate; all these values were within normal limits.

ment. Roentgen therapy had not been applied. The patient had never been circumcised, nor had he ever noticed pruritus or urethral discharge. He had not used contraceptives. There was no history of dysuria or of any impairment of the urinary stream. The patient was not aware of any eruption on the body associated with the present penile lesions.

His past medical history was essentially noncontributory except for the occurrence of urticaria during childhood and a series of "boils," which had left depressed scars, at the age of 17.

The significant physical findings were confined to the skin and the genitalia.

Examination of the Skin.—Approximately two dozen oval, depressed, atrophic scars, ranging in length from 0.5 to 1.0 cm., were revealed on the arms and the trunk. These were the result of furuncles, and biopsy of a specimen of one showed no evidence of lichen sclerosis et atrophicus.

Examination of the External Genitalia.—On the glans penis were two white, dry, glazed areas of atrophy around the lateral and anterior portions of the external meatus, the atrophic plaques covering approximately one third of the

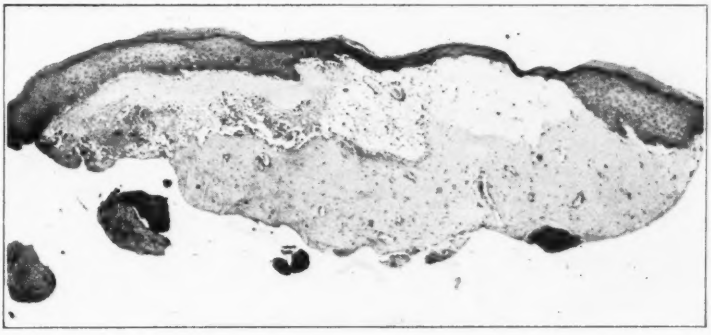

Fig. 2.—Low power view of the tissue removed from a telangiectatic lesion on the glans. Atrophy of the epidermis and dilatation of vessels in the upper part of the corium are notable; the extensive homogenization of the connective tissue is a diagnostic feature.

glans. The atrophic lesions were "crinkled," with an irregular border. On palpation, they felt like thin parchment paper. The ventral half of the meatus was involved in the atrophic process but was sharply demarcated from the dorsal half, which appeared normal. On each side of the meatus, but more extensive on the right side, were several irregular, reddish purple telangiectatic areas. Around the residuum of the frenum several erosions were noted, and the entire inner surface of the prepuce was thickened, inelastic and of a dead white color (fig. 1).

The scrotum and contents were normal. On rectal examination the prostate gland was found to be normal in size and consistency. Proctoscopic examination revealed no abnormal changes in the mucous membrane of the rectum.

Intravenous Pyelography.—The upper part of the urinary tract functioned normally, with no evidence of distortion.

Cystoscopic Examination.—The urethra readily admitted a 26 French sound. The 24 French panendoscope entered the bladder easily. The bladder appeared normal; no stones, tumor or ulceration was noted, and there was no residual urine

or trabeculation. The posterior and anterior portions of the urethra were then carefully observed, and no areas of constriction were noted; the mucous membrane was of normal appearance throughout except for the meatal changes previously noted.

Laboratory Data.—The reaction of the blood serum to the Kahn test was negative. Examination of the blood showed 4,200,000 erythrocytes, 11.0 Gm. of hemoglobin per hundred cubic centimeters (80 per cent) and 6,900 leukocytes, of which 74 per cent were polymorphonuclear cells, 17 per cent lymphocytes, 3 per cent eosinophils and 6 per cent monocytes.

Histologic Observations.—The specimen taken from a telangiectatic area showed hyperkeratosis with occasional areas of parakeratosis; the stratum

Fig. 3.—Dyskeratosis of the epidermis. Note the loss of normal architecture and lack of cellular identity in much of the prickle cell layer, with intracellular edema ("liquefaction degeneration"). The possible beginning of early malignant change is suggested at *X*. The resemblance of clinical and microscopic features to those of roentgen dermatitis is interesting.

lucidum was not seen, and the granular layer was thickened in some places but almost absent in others. The whole epidermis showed moderately advanced atrophy, with almost total loss of rete pegs (fig. 2). In addition to being thin, the prickle cell layer exhibited a dyskeratotic appearance, with intracellular edema more pronounced toward the lower half; many of the prickle cells had lost their individual identity (nuclei and protoplasmic bridges were absent). These changes in the prickle cells and basal cells were apparently what Freeman and Laymon termed "liquefaction necrosis" and Montgomery and Hill called "liquefaction degeneration" (fig. 3). The diagnostic feature of the section was in the dermis,

where the characteristic band of edema and homogenization of the connective tissue were clearly demonstrated. The connective tissue was apparently edematous and hyalinized and had lost almost all nuclei. Just below the basal cell layer, the upper part of the corium showed dilatation of the blood vessels and extravasation of some erythrocytes, lymphocytes and, occasionally, large monocytes. All in all, there seemed to be an actual increase in the total thickness of the connective tissue layer here, as compared with the normal amount in the glans penis. Fibroblasts were seen only deep in the section.

The specimen from a white, atrophic plaque showed more pronounced hyperkeratosis and further advanced atrophy of the epidermis. The wide band of homogenized connective tissue in the upper part of the corium appeared to be

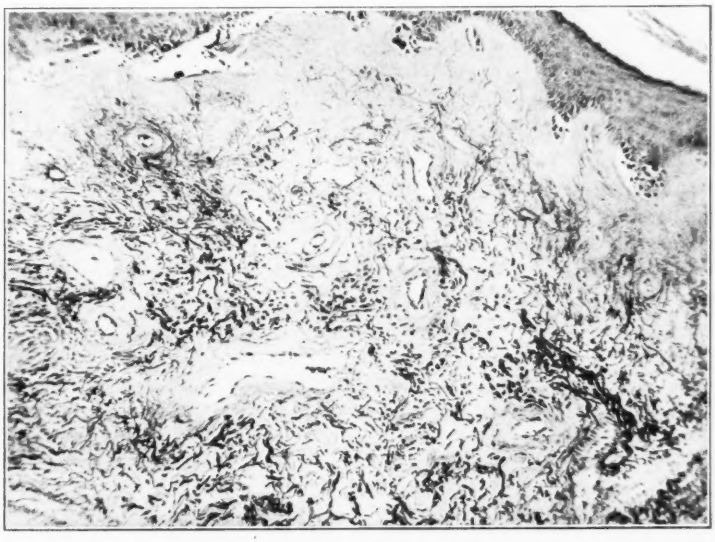

Fig. 4.—Section from the atrophic area of the glans stained with Weigert's resorcinol-fuchsin stain for elastic tissue, showing separation of elastic tissue from the epidermis and almost complete absence of it in the upper corium; splitting and fragmentation of the elastic fibers are seen in the middle and lower parts of the corium (medium power).

more solid and to extend right up to the basal cell layer in places. It was more acellular in its upper portion, where only a few scattered lymphocytes were seen. No definite malignant change was observed in any of the sections (but see fig. 3).

Sections prepared with Weigert's elastic tissue (resorcinol-fuchsin) stain showed separation of the elastic tissue from the epidermis and almost complete absence of these fibers in the homogenized zone. In the midcorium splitting of the fibers was seen; the total amount of elastic tissue appeared to be less than normal (fig. 4).

COMMENT

We have attempted to present a study of a patient with balanitis xerotica obliterans, whose chief complaint was pain during intercourse; this symptom, and the appearance of a "white spot" on the glans, preceded the minor "clipping" operation to which he submitted. Gradual enlargement of the atrophic lesions on the glans occurred, but there was no impairment of his urinary stream. We believe this circumstance is best explained by the fact that the dorsal half of the meatus was still uninvolved and provided sufficient elasticity to permit the passing of a 26 French sound, the equivalent of a normal urinary stream. It is likely that continued progression of the disease process may eventually bring about stenosis.

The histologic observations in our two biopsies are in entire agreement with the published descriptions of this disease and are almost the same as, if not identical with, those of lichen sclerosus et atrophicus as enumerated by Montgomery and Hill.[8] The differential diagnosis was adequately discussed by Freeman and Laymon.[4b] They stated that circumscribed scleroderma can be excluded on microscopic evidence because it presents "an actual increase in the number and thickening of the individual connective tissue fibers throughout the whole cutis as contrasted with the edematous, homogenized zone in the upper cutis of balanitis xerotica obliterans." One would also expect to find a greater loss of elastic tissue fibers in scleroderma. Leukoplakia can be differentiated by the fact that it is essentially a hypertrophic, hyperplastic process. By contrast, lichen planus atrophicus shows a characteristic bandlike, dense cellular infiltrate in the subpapillary layer. Lichen sclerosus et atrophicus and balanitis xerotica obliterans are, in Freeman and Laymon's opinion, one and the same disease.

There was no clue to possible etiologic factors in our patient's history; we believe the disease began prior to his operation and that it was not influenced by the "clipping" procedures. In the majority of cases recorded in the accompanying table there had been no preceding operation; Reif also reported 2 cases in which there had been no operation.[9] Why such a degenerative process should localize on one small area of the body is an intriguing puzzle. It is possible that the pathologic process begins in the upper part of the corium, with involvement of the blood vessels there. This is suggested by the fact that the most drastic changes are observed immediately above and, particularly, just below this zone. Biopsy of two specimens in our case showed that the telangiectatic

8. Montgomery, H., and Hill, W.: Lichen Sclerosis et Atrophicus, Arch. Dermat. & Syph. **42**:755 (Nov.) 1940.

9. Reif, F. B.: Balanitis Xerotica Obliterans, Correspondence, Arch. Dermat. & Syph. **49**:304 (April) 1944.

lesion contained more dilated vessels in the upper part of the corium and in general presented a less advanced state of atrophy and degeneration than did the white plaque.

The principal therapeutic objective is maintenance of an adequate urethral meatus; in some of the cases reported, surgical excision of part of the involved tissues was necessary to accomplish this. Circumcision alleviated the symptoms in several cases; in others, periodic dilation with sounds was sufficient. Our patient has been given testosterone propionate by intramuscular injection at weekly intervals and also by local inunction; over a period of ten weeks this treatment has brought about no improvement. So far as we know, the endocrine approach in therapy is on an empiric basis.[10] It is hoped that further study of this condition will lead to more effective therapy.

SUMMARY

Balanitis xerotica obliterans is a disease of interest to urologists as well as dermatologists. Meatal stenosis, with impairment of the urinary stream, or pain on intercourse is more likely to make the patient seek treatment than is a simple white lesion on the glans penis. The invasion of the urethral mucous membrane by this process, which starts in the skin, led us to wonder about the possibility of associated lesions in the genitourinary tract; none were found. The principal observations in the cases reported thus far in the American literature are tabulated. The report of a case including results of a complete urologic examination (by P. N.) and of biopsies of specimens from the glans penis, with brief comment on treatment, is presented.

NOTE.—On March 4, 1945, circumcision was performed on the aforementioned patient by one of us (P. N.). Even though part of the incision was necessarily carried through the affected foreskin, healing occurred readily during the first week after operation. Microscopic examination of the tissue removed showed changes identical with those found at our previous biopsies. The patient is now able to have intercourse painlessly and is well pleased. The lesion around the meatus remains unchanged.

Dr. T. H. Byrnes assisted in the histologic study, and the staff of the Heineman Foundation (Charlotte Memorial Hospital) prepared the photomicrographs.

403 North Tryon Street (Dr. Welton).

The Nalle Clinic, 412 North Church Street (Dr. Nowlin).

10. The most one could reasonably expect from this treatment would be to arrest the degenerative process. However, the mechanical obstruction which the fibrotic band in the prepuce presents on erection of the penis can be removed only by surgical intervention; circumcision has been advised for this patient.

ROENTGEN THERAPY FOR HYPERHIDROSIS

Observation of One Hundred and Twenty-Two Patients

J. BORAK, M.D.†
J. J. ELLER, M.D.
AND
W. D. ELLER, M.D.
NEW YORK

AFTER the discovery of L. Freund (1897) that roentgen rays can produce a loss of hair, the reaction of the other elements of the skin became an object of investigation. One of the earliest observations was that skin which because of some pathologic condition was exposed to the rays would become dry. Pusey,[1] in 1901, drew from this observation the conclusion that roentgen therapy might be effective in the treatment of local forms of hyperhidrosis. Stelwagon,[2] in 1903, appears to have been the first to report a case of hyperhidrosis in which roentgen therapy produced a "pronounced lessening of the secretion, and this without producing any unpleasant x-ray effects."

Since that time roentgen therapy has maintained its position as an effective remedy against excessive perspiration. One of us (J. J. E.),[3] in 1938, summed up his experience as follows: "Roentgen rays are the most efficacious remedy in combatting extensive sweating of localized areas." MacKee and Cipollaro,[4] in 1946, asserted, "It is now admitted that roentgen therapy will not only overcome excessive sweating in localized areas, but that such a procedure constitutes the only certain method of permanently curing the condition."

The experience shows, however, that in practice roentgen therapy is much less frequently used in hyperhidrosis than might be expected in the light of the above reports.

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† Dr. Borak died on April 2, 1949.

From the Skin Division of the New York City Hospital, service of Dr. J. J. Eller.

1. Pusey, W. H.: Roentgen Rays in the Treatment of Diseases of the Skin, J. A. M. A. **37**:820 (Sept. 28) 1901.

2. Stelwagon, H. W.: J. Cutan. Dis. **21**:345, 1903.

3. Eller, J. J.: Roentgenotherapy in Diseases of the Skin, in Pohle, E. A.: Clinical Roentgen Therapy, Philadelphia, Lea & Febiger, 1938.

4. MacKee, G. M.; and Cipollaro, A. C.: X-Rays and Radium in the Treatment of Diseases of the Skin, ed. 4, Philadelphia, Lea & Febiger, 1946.

Of twenty-five certified specialists of the American Board of Dermatology questioned about their experience with roentgen therapy for excessive perspiration only three qualified it as "excellent or very good." Eight declared that roentgen therapy helped "often or sometimes." Fourteen of these specialists—thus, the majority—admitted that they neither used nor recommended roentgen irradiation for this condition because, in their opinion, cessation of hyperhidrosis by roentgen therapy could not be obtained without damage to the skin.

During the war the United States Army did not accept for military service men suffering from excessive perspiration of their palms because the disease was considered incurable.

The Journal of the American Medical Association, on Nov. 10, 1945, published the following reply to a query concerning roentgen therapy for hyperhidrosis:

> The amount of x-ray therapy needed to control hyperhidrosis of the palms and soles is relatively large. The skin is probably damaged by it. When successful, there is often abnormal dryness and changes more or less characteristic of a radiodermatitis. The latter may not appear until years later. This should be enough to decide against x-ray therapy.[5]

The unfavorable opinions about the value of roentgen therapy in hyperhidrosis are, we feel, solely the result of the employment of an inadequate technic of irradiation. With adequate technic the results are, as will be shown in this paper, both safe and dependable.

SIGNS AND SYMPTOMS

According to Robinson,[6] who examined a number of sections from the palms, no abnormal findings were present in the epithelial cells of the sweat glands of hyperhidrosis. Therefore hyperhidrosis has been generally considered a purely functional disorder. The palms, axillas and soles, in this order, are the most frequently affected areas. Hyperhidrosis of the palms comes often in combination with that of the feet. This combination is more frequent than that of hyperhidrosis of the palms with that of the axillas. The combination of hyperhidrosis of the feet with that of the axillas has not occurred in our experience. In about 7 per cent of our cases all three areas were affected. All other regions of the body, such as the dorsal surface of the feet, the back and the forehead, are only infrequently the site of hyperhidrosis.

Hyperhidrosis occurs with almost the same frequency in men as in women. However, the distribution is not the same in both sexes. While hyperhidrosis of the palms is approximately as frequent in men

5. X-Rays for Hyperhidrosis, Queries and Minor Notes, J. A. M. A. **129**:776 (Nov. 10) 1945.

6. Robinson, A. R.: A Manual of Dermatology, New York, D. Appleton & Co., 1885.

as in women, it occurs in the feet almost twice as frequently in men as in women, and in the axillas eight times as frequently in women as in men. In addition, hyperhidrosis of the axillas in men is, as a rule, combined with that in another area, while in women frequently only the axillas are affected.

Our youngest patient was 14, and the oldest, 41. Seventy-one per cent of our patients were less than 30 at the time of their first treatment. From this observation it would seem to appear that, beginning with the fourth decade of life, the activity of the sweat glands has a tendency to lessen.

It is of interest that 62 per cent of our patients, irrespective of their national origin, were of light complexion and blond or light eyed or both. Patients with dark skin, hair and eyes were in the minority. We had no opportunity to treat patients with yellow or black skins for hyperhidrosis.

The skin in the areas of the excessive perspiration is usually "moist, cold and clammy."[7] Parkhurst described localized lividities on the heels. Constantly macerated, the skin is tender and may become thickened and sodden. There is a tendency toward the formation of callosities on the soles. Occasionally there is dermatitis, intertriginous eczema or exfoliation of the epidermis, often associated with itching. Furuncles may develop in the axillas.

The patients with hyperhidrosis react to the sweat-producing stimuli in the same manner as do normal persons. Thus, their secretion increases in quantity when the temperature rises, when their activity is increased or when they are submitted to stronger emotional stimuli. The essence of the disorder lies in an abnormally low threshold of the irritability of the sweat glands. A patient who suffers from hyperhidrosis perspires as profusely at a normal temperature as does a normal person at a high temperature. A patient with hyperhidrosis engaged in light activity perspires as intensely as does a normal person engaged in heavy activity. Finally, under nervous stimuli which do not disturb normal people a patient with hyperhidrosis perspires as excessively as do normal persons when in a state of great anxiety or other emotional strain.

There is, however, no lower threshold toward sweat-producing or sweat-inhibiting chemicals, such as pilocarpine or atropine.

Patients with hyperhidrosis perspire less when the temperature drops, when they rest and when they are not emotionally affected. Therefore, it is characteristic that no excessive perspiration in the affected areas occurs during the patient's rest at night, this fact being a criterion in differential diagnosis of the excessive sweating in hyperhidrosis and that in various internal diseases.

7. Eller, J. J.: M. Rec. **154**:167, 1941.

During the day the affected areas are, because of the lowered threshold of their excitability, almost constantly wet. When the condition is more pronounced, there is also an intermittent formation of drops of sweat. The hands drip with water, often forming small lakes where the water falls. The patients often carry blotters in order not to soil the paper when they write. They often leave a mark on any book or furniture they touch. Gloves are rapidly soiled, and stockings and shoes become soaked with secretion. Shirts rapidly become wet, and often so do the other clothes, sometimes even the coat. The perspiration of the soles and the axillas is often associated with an offensive odor because the sweat cannot evaporate and subsequently undergoes chemical decomposition.

These effects are consequential from the social standpoint. A number of our patients complained that their excessive perspiration was the reason that they were socially avoided by many persons and, sometimes, rejected by their prospective marriage partners.

Hyperhidrosis also causes economic hardships. Perfumed soaps, deodorants and antisudorific preparations must often be used. Stockings, shoes, gloves, shirts and other clothes must be changed more frequently than usual. Hand workers, such as physicians, dentists, pianists and tailors, are often severely handicapped.

To "social quarantine and economic isolation" (Kahn)[8] mental strain may be added. A vicious circle develops. Nervous stimuli increase the nervousness. Many of our patients suffered from anxiety at the thought of having to shake hands. Some were haunted even in their dreams by this feeling. These persons tend to become shy and depressed and to suffer from feelings of inferiority.

ANATOMY AND RADIOBIOLOGY

The anatomy of the sweat glands, glandulae sudoriferae, was first established by Purkinje in 1833. Ranvier, in 1899, distinguished the sweat glands (merocrine) from the sebaceous glands (holocrine). The merocrine glands have only a single layer of epithelium and form their secretion, enlarging during the period of the formation of the secretion and becoming smaller after the secretion has been poured out.

The holocrine glands are made up of several epithelial layers. A structural transformation of the cells takes place while the deeper cells come to be transferred to the surface, as a result of which development the secretion is formed.

The transformation in the sebaceous glands resembles that in the hair and in the epidermis, while the epithelium of the sweat glands behaves like the endothelial cells of the capillaries or the fibrous tissue.

8. Kahn, K.: New York State J. Med. **45**:1555, 1945.

The main difference is that the holocrine glands continuously degenerate and regenerate, while the merocrine glands preserve their anatomic structure. This fact accounts for the difference in radiosensitivity between the holocrine and the merocrine tissues.

One of us (J. B.)[9] found that the sweat glands are much less radiosensitive than are the sebaceous glands. With a single exposure, the lethal dose for the sweat glands is 2,400 r, and that for the sebaceous glands, 1,200 r (tissue roentgens). The sweat glands have been found in microscopic sections to be less radiosensitive than the hair follicles and the epidermis, also.

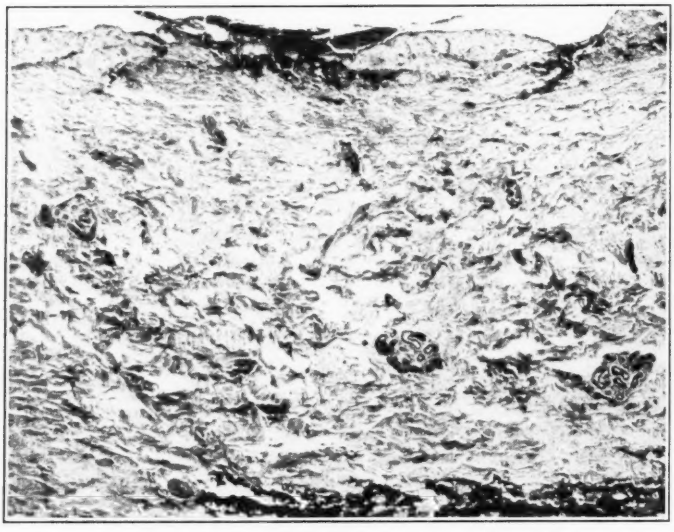

Fig. 1.—The epidermis, the sebaceous glands and the hair follicles have been destroyed by roentgen rays. The sweat glands are still well preserved.

Figure 1 illustrates the fact that a dose of rays which completely destroyed the sebaceous glands, the hair follicles and the epidermis —by so doing producing the so-called moist epidermitis or epidermolysis—still left the sweat glands anatomically well distinguishable.

The opposite impression, namely that the sweat glands are more radiosensitive than are the other epithelial elements of the skin, results from the observation that roentgen rays may reduce the activity of the sweat glands without any visible alteration of the skin. Even the sweat glands themselves may show no anatomic changes. This point

9. Borak, J.: Radiology **27**:651, 1936.

was first noticed by Buschke and Schmidt,[10] who, in 1905, to their surprise, observed in cats a cessation of the secretory activity of the sweat glands after treatment with roentgen rays while examination of the excised skin showed the sweat glands to be of normal appearance.

Closer investigations, however, have revealed that a cessation of the secretory activity without anatomic changes of the sweat glands is only temporary. After some time, usually within several months, the sweat glands begin to resume their activity. Our studies warrant the conclusion that a permanent cessation of the secretion of the sweat

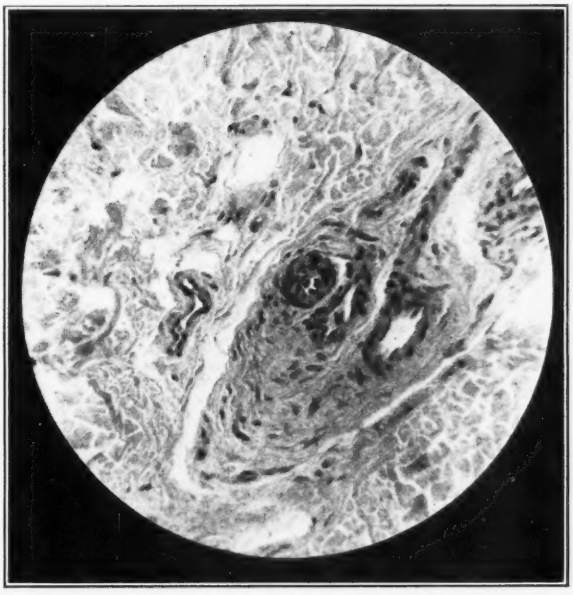

Fig. 2.—Atrophy of the sweat glands eight years after the irradiation.

glands cannot be obtained without anatomic alterations in the secretory cells of the sweat glands. It is not necessary that the sweat glands be entirely destroyed, as is done when a cancerous growth is treated with roentgen rays. It is, however, required that an irreparable cell atrophy result if the cells are to remain permanently in a state of secretory inactivity. Such a result is illustrated in figure 2. The material was obtained from a physician who, grateful for his cure, permitted a specimen of the irradiated area of the left palm to be taken with a biopsy punch, eight years after the irradiation.

10. Buschke, A., and Schmidt, H.: Deutsche med. Wchnschr. **13**:495, 1905.

Anatomic changes, such as those illustrated in this case, may be observed only years after the irradiation has been terminated. Following the roentgen ray treatment, first, various degenerative alterations occur (see figure 3) and slowly progress to the point of atrophy. Just as the lack of spontaneous degeneration explains the low radiosensitivity of the sweat glands, so does the lack of spontaneous regeneration account for the progressive nature of the anatomic alterations, once they have been induced by roentgen rays.

It is interesting to note that, while the vast majority of the sweat glands in the irradiated area may show pronounced anatomic changes, some of the glands may appear morphologically normal. This fact was first observed by Rost,[11] in 1915. He found the same phenomenon also in other irradiated tissues and referred to it as the "spot-like" mode

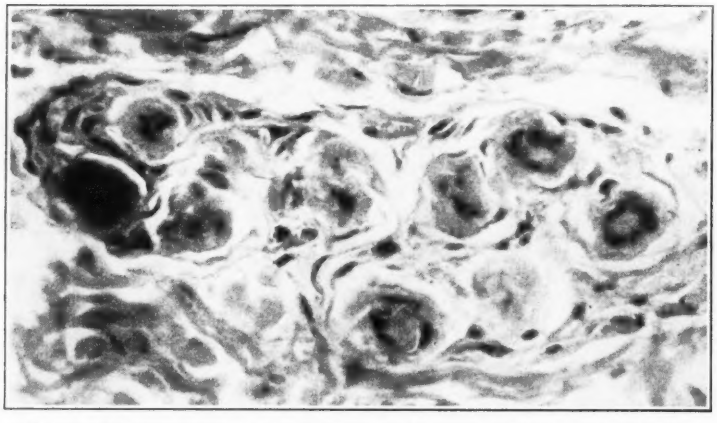

Fig. 3.—Various stages of degeneration of the sweat glands after irradiation.

of roentgen ray action. This mechanism, which, incidentally, accounts for late recurrences of cancer from cells which have survived irradiation, might explain the fact that, even in patients cured of hyperhidrosis, the skin may remain capable of producing some secretion when exposed to high temperatures or other exciting stimuli.

With the state of the atrophy of the sweat glands there is invariably associated an elimination of the sebaceous glands and an effluvium of hair in the hairy areas, such as the axillas. The alterations of the other elements of the skin, such as the epidermis, the blood vessels and the connective tissue, depend on the technic of irradiation. With an adequate technic, the microscopic changes in these tissues are only

11. Rost, G. A.: Strahlentherapie **6**:269, 1915.

temporary and no clinically significant alterations, such as dermatitis, atrophy or telangiectasia, occur, as far as can be concluded from our experience thus far.

TECHNIC OF IRRADIATION

The total dose required to produce an atrophy of the sweat glands is, in our estimation, about 40 per cent of the dose required to cure a small basal cell cancer. When filtered rays are used, such a dose can be applied without any visible reaction of the skin. This situation results from the fact that the more the rays are filtered, the larger are the amounts of radiation that can be given without producing erythema. While the average skin erythema dose is 300 r with unfiltered rays, it is 550 r with a 3 mm. aluminum filter (MacKee and Cipollaro).[12] The use of the unfiltered rays is, in our opinion, the most important cause of failures in roentgen therapy of hyperhidrosis. In order for cutaneous reactions to be avoided, smaller single doses are applied when unfiltered rays are used. This procedure does not take into account the low radiosensitivity of the sweat glands and the necessity of inducing pronounced anatomic changes if a permanent cessation of the sweat secretion is to result. Since the sweat glands are the least radiosensitive epithelial element of the skin, the single doses must be large enough to produce the necesary anatomic changes. This statement is particularly true with regard to the first treatment, which must have a pronounced effect, so that the succeeding treatments may accumulate. Customarily, when a larger initial dose is given, the treatment is repeated only after an interval of several weeks. This method, however, weakens the cumulative effect of the first treatment, so that a larger number of treatments is required to make up for the recovery of the irradiated tissue during the rest period. The cumulative effect can, however, be maintained, as has been shown by the saturation method of Kingery and Pfahler, if smaller doses are added after shorter intervals. In order for one to ascertain that there would be no unfavorable reaction as a result of previous treatment, the irradiated skin should be carefully observed and the patient interrogated as to any unpleasant sensations before a new treatment is given. No further treatment is needed if there is a 75 per cent improvement in the condition.

Thus, we have arrived at the following standard formula: Through a filter of at least 2 mm., and preferably 4 mm., of aluminum, a dose of 300 r in air is given, and half of this dose is added twice at intervals of ten days. (When the additional treatments were given in less than ten days, some patients experienced a drawing sensation.) This series of treatments is repeated, if necessary, in the same manner after a period of four weeks.

12. MacKee, G. M., and Cippolaro, A. C.: Roentgen Dosage in Dermatology Expressed in International Roentgens, Arch. Dermat. & Syph. **41**:1 (Jan.) 1940.

Thus, a total dose of 1,200 r in air (about 1,600 r on the skin) is administered in six sessions within a period of about eight weeks. The distance between the focus and the skin is 35 cm. for the treatment of the axillas, 35 to 40 cm. for the treatment of the palms and 40 to 45 cm. for the treatment of the soles, the exact distance depending on the size of the field. The treatments can be given with 100 kilovolt machines, but the time of the irradiation is considerably shortened with higher kilovoltages, such as 140 kilovolts, when a filter of 4 mm. aluminum is used.

Careful attention was given to the blond patients, who were predominant in our series. It was found that they tolerated the above doses rather well.

RESULTS OF ROENTGEN THERAPY

This report is based on the observation of 122 patients who had been suffering from continuous excessive perspiration of the palms, feet or axillas. From two years to eighteen years have elapsed since the termination of treatment of each patient. Our results were highly satisfactory. Thus far, in not a single patient has any evidence of roentgen ray injury to the skin been observed. With the technic applied, even the blond skins seem to tolerate the dosage well. All patients have shown pronounced improvement, which, as a rule, was noticed about three weeks after the first series of treatments. For a large number of patients in this series the results were so satisfactory that no further treatment appeared necessary.

SUMMARY

On the basis of our experiences we believe that, properly applied, roentgen therapy is the best method of treating hyperhidrosis.

The skin should be examined carefully and the patient interrogated after each visit. Age, sex and complexion of the patient and location of the hyperhidrosis are factors which should be taken into consideration.

In order for excessive dryness of irradiated areas to be avoided, treatment should be discontinued after a 75 per cent improvement. No more than two series of treatments should be given.

In our series of 122 patients, with blond skins as well as brunet skins, there was no sign of irritation, reactions or sequelae from the doses of roentgen rays administered as described herein.

The absence of roentgen ray injury to the skin in our cases is to be attributed to the filtration used.

The use of unfiltered rays is the most important cause of failures in roentgen therapy of hyperhidrosis.

745 Fifth Avenue (Dr. J. J. Eller).

PERSISTENT MULTIPLE HERPES-LIKE ERUPTION

Response to Repeated Intradermal Injections of Smallpox Vaccine

LEONARD E. SAVITT, M.D.
AND
SAMUEL AYRES Jr., M.D.
LOS ANGELES

THE case reported by us is of unusual interest because of an apparently specific response to vaccine therapy which may open a new trend in treatment of dermatoses that we suspect but cannot prove to be of virus origin.

Clinically the case has been a peculiar one, corresponding in many ways to one of impetigo herpetiformis. The lesions were located on the scalp and neck, the upper portion of the chest, the back, the lips and the buccal mucosa and consisted essentially of grouped vesicopustules that became crusted and spread in a circular manner. Removal of the crusts left raw, denuded areas. Clearing of individual patches occurred spontaneously, leaving lightly pigmented macular areas without clinical evidence of scarring. Incomplete generalized clearing occurred at about six week intervals. Most remissions were preceded by conjunctivitis. Recurrences of the eruption were limited in most instances to areas above the middle part of the chest.

REPORT OF A CASE

R. S., a 10 year old American-born white boy, referred by Dr. L. M. Earle, was first seen by us on Feb. 25, 1946, complaining of reddened irritated areas on the lips, in and around the eyes and behind the left ear, which lesions had been present intermittently for one and a half years.

Prior to the development of the dermatosis the patient's throat had become sore and his ankle had become "irritated" after minor trauma. After injection of an undetermined amount of penicillin the irritation of the ankle had disappeared.

The patient had been hospitalized on two occasions, for a total time of several months.

Past History.—In the past history were attacks of sinus disease, tonsillectomy in early childhood, intermittent temperatures of from 2 to 4 degrees above normal for one and a half years, pyuria in April 1945 and infection of the throat in 1940, stated to have been caused by a streptococcus and treated successfully with a sulfonamide compound. The patient had had urticaria and angioneurotic edema for several years, up to two years, before we saw him.

Examination.—Examination at the time of the first visit revealed a peculiar symptom complex. The lesions, which covered the entire vermilion surface of both lips and extended into the mouth and onto the gums, buccal mucosa and pharynx,

consisted of tiny superficial white ulcerations which were cobblestone-like and raw. Involvement of both eyes consisted of redness and crusting of the eyelids, congestion of the medial portion of the left eyeball and crusting of both eyebrows. Behind the left ear there was an eruption consisting of pinhead to pea-sized vesicopustules and a dime-sized "raw" area with a vesicopustular border. The cervical, retroauricular and axillary lymph nodes were enlarged. Three small

Fig. 1.—R. S. in October 1945.

crusted lesions were present on the back of the neck, and a few were seen on the legs. Ill defined, superficial, slightly pigmented and scarlike lesions could be seen where the eruption had cleared.

The following treatment was not effective: dilute dalibour water (water containing zinc and copper sulfates) compresses to the ears, petrolatum U. S. P. to the legs and 5 per cent boric acid ointment to the eyelids; fourteen semi-

weekly injections of 2 cc. of liver injection U. S. P. intramuscularly; a preparation of vitamin B complex; penicillin troches; tablets of methenamine and sodium biphosphate N. F., 5 grains (0.32 Gm.) of each, three times a day; six biweekly vaccinations for smallpox by the scratch method; semiweekly injections of autogenous staphylococcus vaccine, graduating from 15,000,000 to 300,000,000 killed organisms, prepared from a culture of material taken from pustules on the forehead; sulfadiazine and sodium bicarbonate, 7½ grains (0.48 Gm.) four times a day; nine intravenous injections of 5 cc. of calcium thiosulfate and nine intramuscular injections of 1 cc. of parathyroid injection U. S. P.; sulfamerazine, 15 grains (0.97 Gm.) every six hours for one day; intraderm tyrothricin solution® (a skin-penetrant solution containing 1 mg. of tyrothricin per cubic centimeter in a base of surface-active agents, organic solvents and water) applied locally; pyridoxine hydrochloride, 25 mg. three times a day by mouth; tripelennamine hydrochloride (pyribenzamine hydrochloride®), 25 mg. four times a day; one injec-

Fig. 2.—Annular vesicular lesions present in February 1946. At that time there was also photophobia.

tion of 0.5 Gm. of sodium iodide intravenously; ferrous sulfate, 10 grains (0.65 Gm.) three times a day by mouth; twenty-one semiweekly intravenous injections of 100 mg. of pyridoxine hydrochloride; nine semiweekly intramuscular injections of 1 cc. of solu B® (thiamine hydrochloride, 10 mg.; riboflavin, 10 mg.; pyridoxine hydrochloride, 5 mg.; calcium pantothenate, 50 mg., and nicotinamide, 250 mg.); folic acid (pteroylglutamic acid), 5 mg. three times a day by mouth; vitamin A, 50,000 international units three times a day, and diphenhydramine hydrochloride (benadryl hydrochloride®), 50 mg. three times a day.

Lesions subsided almost completely soon after the onset of twenty-four daily intramuscular doses of 300,000 units of penicillin injection in oil and wax U. S. P. (7,200,000 units total), but began to recur during the last few injections. This recurrence was said to have taken place in a similar manner after injections of penicillin on occasions previous to the patient's being seen by us. In vitro tests

of sensitivity to penicillin showed that the organism recovered in April 1947 did not grow in the presence of 12 units of penicillin per cubic centimeter. The organism recovered in September 1947 was not inhibited by 100 units per cubic centimeter.

The patient was referred to virologist Harold Pearson, M.D., of Los Angeles County General Hospital, who inoculated the fluid from a pustule onto a rabbit's corneas and the chorioallantoic membranes of a chick embryo, with no reaction.

Consultation with an otorhinolaryngologist revealed moderately infected adenoids and allergic rhinitis. Roentgenologic examination revealed "complete obliteration of the haustral markings of the colon, indicative of a profound deficiency state."

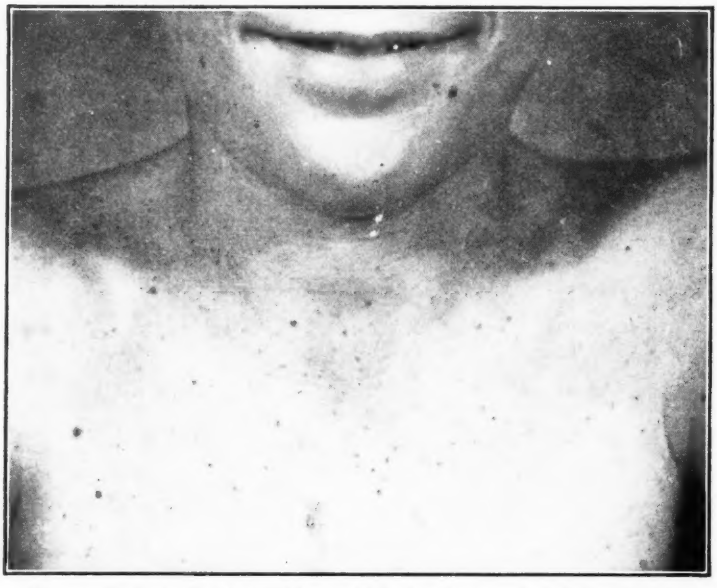

Fig. 3.—R. S. in October 1947, at which time he was free from lesions.

Effective Treatment with Vaccine.—The intradermal injection of the contents of one capillary tube of a commercial smallpox vaccine [1] was instituted Jan. 16, 1947, and repeated at two to four day intervals. The first definite sign of improvement was noted on February 10, three days after the seventh injection. There was no reaction to the first injection, but a vaccinial type of reaction followed the second injection. Subsequent reactions decreased in severity; consequently the contents of two capillary tubes of vaccine were injected each time, starting February 10. Some scattered new lesions occurred after the tenth injection. On February 27, after twelve injections, the skin was almost completely clear, no active lesions being seen. On March 8, after the fourteenth injection and fifty-one days after the first injection, the skin was entirely clear.

1. The vaccine used differed from U.S.P. specifications only in that brilliant green dye was added, with the intention of lowering the bacterial count.

Injections were stopped. Nineteen days later a few vesicles appeared about the face and upper gums. There was a twenty-four day interval between the fourteenth and the fifteenth injection, thereafter only a one week interval and subsequently a two week and then a three week interval. The last lesion a single vesicle, occurred on May 9, 1947. Till the time of writing, forty-two injections have been given, the last one on Dec. 26, 1947, at which time the skin was entirely clear.

Laboratory Examinations.—The results of laboratory examinations were as follows: Gram's stain of material from lesions revealed mucus and staphylococci. The red blood cell count was 4,190,000, and the white blood cell count, 15,000, with a differential count of 45 neutrophils, 3 stab cells, 32 lymphocytes, 13 monocytes and 10 eosinophils per hundred cells, the amount of hemoglobin being 71 per cent and the color index 0.86. The urine was normal, and the reactions to scratch tests with allergens were all negative. Cultures from lesions on the neck revealed Staphylococcus albus; those from lesions of the gums, Streptococcus aureus and Streptococcus viridans and spirilla and fusiform bacteria, and cultures from lesions of the palate, Staphylococcus aureus. The level of serum calcium was 8.98 mg. per hundred cubic centimeters; of chloride (as sodium chloride), 479 mg., and of sodium, 320 mg.

A specimen for biopsy was not taken.

COMMENT

This case is reported because of the dramatic improvement following therapy consisting of repeated intradermal injections of smallpox vaccine, particularly as contrasted with the lack of success of a limited number of smallpox vaccinations performed by the usual scratch method.

The technic used was a variation of that used by Arnold.[2] Approximately 0.1 cc. of an isotonic solution of sodium chloride is drawn into a tuberculin syringe with a no. 24 or no. 25 hypodermic needle (½ inch [1.2 cm.]) attached and then is mixed in the syringe with the contents of one capillary tube of smallpox vaccine. The intradermal injections may be made anywhere, but a site near the deltoid muscle is preferable.

The use of smallpox vaccine administered intradermally for routine prophylaxis of smallpox is now accepted by public health authorities.

It is known that no distinct parallel occurs between resistance to virus dermatoses and the presence of serum antibodies.

The unknown mechanism of response to therapy in the reported case probably parallels that occurring in herpes simplex and aphthous stomatitis and the protection afforded in smallpox.

There may be antigenic differences in the herpetic strain. Some strains of smallpox may have an antibody common to some strains of herpes simplex.

In general, attempts to immunize against herpes simplex by the use of strains of herpes simplex virus have not been successful.

2. Arnold, H. L., Jr.: Herpetic Stomatitis Treated by Intradermal Smallpox Vaccine, Proc. Staff Meet. Clin. Honolulu **10**:85-89 (Aug.) 1944.

SUMMARY

A generalized herpes-like eruption affecting a 10 year old boy remained refractory to many forms of therapy for a period of about two and a half years, this condition resulting in partial to complete disability for varying periods of time. The institution of repeated intradermal injections of smallpox vaccine resulted in distinct improvement in four weeks, almost complete improvement in six weeks and complete absence of lesions in seven weeks. With continued injections the patient remained free of lesions for eight months, up to the time of writing.

We believe that the term "herpes multiplex" would most aptly fit the described condition.

4036 Wilshire Boulevard (Dr. Savitt).

2007 Wilshire Boulevard (Dr. Ayres).

Clinical Notes

A BULLOUS ERUPTION ASSOCIATED WITH CARCINOMA OF THE PENIS

JOHN M. SIEGEL, M.D.
ALLENTOWN, PA.

Except for those on acanthosis nigricans, observations on cutaneous manifestations of malignant visceral tumors are not common. In 1922 Davis [1] reported on 2 patients with exudative erythema associated with malignant diseases of the uterus. One had a spindle cell sarcoma of the uterus, the eruption clearing shortly before death; the other had a uterine adenocarcinoma, the eruption disappearing promptly after curettage. Becker, Kahn and Rothman [2] in 1942 reviewed the literature and reported cutaneous lesions in 2 women who had died of internal malignant tumors, discovered at autopsy: one a neoplasm of the pancreas, and the other a carcinoma of the stomach. In both patients the subjective symptoms were referable to the skin. In a survey of the literature, Becker and associates found only 8 case reports since 1925 demonstrating a relation between dermatoses and malignant tumors. These reports confirmed previous observations [3] that internal neoplasms may be responsible for pruritus, hyperpigmentation, toxic bullous eruptions and epidermal hyperplasia (acanthosis nigricans).

REPORT OF A CASE

A. S., an Italian-born man aged 64, was admitted to Bellevue Hospital on July 5, 1946, because of a widespread bullous eruption of a month's duration. It had begun in the groin as small blisters, gradually spreading to the trunk, neck and axillas. There was no history of the use of drugs, either externally or internally. The eruption was mildly pruritic, especially at night. About two months prior to admission the patient had had a penile sore, followed in a week by a painless mass in the left groin. Since the onset of the penile lesion, the patient stated that he had lost about 30 pounds (13.6 Kg.). He gave a history of two similar bullous episodes, each having lasted several months, which he had attributed to "poison ivy."

Physical Examination.—The patient was fairly well developed. He was alert and answered all questions intelligently. There was a generalized bullous eruption, involving the face (particularly about the inner canthus of both eyes and the upper eyelids), the neck, the axillas, the lower portion of the abdomen, the penis, the inguinal regions and the popliteal fossae. Many of the bullae had thin walls, were moderately tense and arose from apparently normal skin; others were surrounded by inflammatory erythema.

From the Department of Dermatology and Syphilology, New York University College of Medicine, and the Dermatologic Service of the Third (New York University) Medical Division, Bellevue Hospital, service of Dr. Frank C. Combes.

1. Davis, H.: On Two Cases of Exudative Erythema Associated with Malignant Disease of the Uterus, Brit. J. Dermat. **34**:12-16 (Jan.) 1922.

2. Becker, S. W.; Kahn, D., and Rothman, S.: Cutaneous Manifestations of Internal Malignant Tumors, Arch. Dermat. & Syph. **45**:1069-1080 (June) 1942.

3. Rothman, S.: Ueber Hauterscheinungen bei bösartigen Geschwülsten innerer Organe, Arch. f. Dermat. u. Syph. **149**:99-123, 1925.

The foreskin was edematous, and protruding through the phimotic opening of the preputial cavity was a dirty, gray, necrotic, vegetative mass measuring about 2.5 by 3 cm. In the left inguinal region was a solid, nontender, globular mass about 4 by 5 cm. in diameter. The physical condition was otherwise essentially normal except for a moderate amount of pitting edema about the ankles.

Laboratory Examination.—The ascorbic acid (vitamin C) content of the blood was 0.49 mg. per hundred cubic centimeters. The content of one of the bullae was examined; of 11 cells, 6 were polymorphonuclear leukocytes, 2 eosinophils and 3 lymphocytes. Repeated blood counts during hospitalization revealed a fluctuating leukocytosis, the count reaching 20,900; a rapidly increasing anemia, and a decreasing eosinophilia. Several months after admission, the number of eosinophils was within normal limits. Tentative diagnoses at the time of admission were (1) pemphigus vulgaris, (2) possible direct left inguinal hernia and (3) hypoproteinemia, manifested clinically by edema of the ankles.

Ophthalmic Examination.—Because of lesions about the eyes, the patient had an ophthalmologic examination, but the only finding was a collapsed bulla of the palpebral conjunctiva of the right lower lid. The consultant offered the opinion that the patient had ocular pemphigus.

Course of Illness.—Several days after admission, the patient had a low grade, intermittent fever and appeared mildly toxic. Treatment was directed against his possible pemphigus. He received daily potassium permanganate baths; local applications of acriflavine-petrolatum gauze; carbarsone, the daily dose beginning with 250 mg. and increasing to 750 mg.; a high vitamin, high caloric diet, and large doses of protein hydrolysate by mouth. Several courses of penicillin in aqueous solution, administered intramuscularly, were also given.

The report on a biopsy made several days after admission was "histologic changes similar to those seen in erythema multiforme bullosum."

The mass in the left groin grew steadily larger and to several observers seemed fluctuant. About one month after admission, a dorsal slit was made on the penis and disclosed a large, foul, necrotic, vegetative mass covering the glans. The tumefaction in the groin was also incised. Sections taken from both the penile and the inguinal lesion proved to be squamous cell carcinoma. However, the pathologist was uable to tell which specimen came from the primary and which from the metastatic lesion.

Because of the profuse, generalized eruption and the rapidity of growth and metastasis of the neoplasm, the surgical consultant advised against radical operation. Plasma and whole blood transfusions were given, without benefit, new hemorrhagic bullae appearing daily. High voltage radiation therapy was then started. For a month no change was noted; the eruption continued, and the secondary malignant growth in the left groin slowly enlarged. The general appearance of the patient was poor; he became weak, pale and cachectic. However, about nine weeks after admission, fewer bullae were noted, and by September 23, eleven weeks after admission, the bullous eruption had disappeared entirely.

High voltage roentgen therapy and radium packs were employed until October 16, at which time the growth had progressed to such an extent that there was no possibility of radiologic control. The patient was weaker, had lost about 75 pounds (34 Kg.) and was extremely anemic and emaciated. He died on Feb. 9, 1947, approximately seven months after admission. During the last four and one-half months he had been entirely free of the bullous eruption which had been his chief complaint on admission.

COMMENT

Most observers considered the eruption secondary to the malignant growth and not pemphigus vulgaris, as was the original opinion. The patient's well-being on admission (despite a history of loss of weight), the absence of oral lesions, the histologic report and the history of the onset of the eruption after the penile lesion had been noted, all favored a diagnosis of erythema multiforme bullosum. Bearing in mind the patient's previous bullous episodes, one might speculate that a bullous eruption was his peculiar method of reacting to "emboli of toxic products." Certainly, in this patient such "toxic products" must have been present in large amounts, if one may judge from the size of the necrotic, putrefying malignant growth.

Becker and associates [2] stated the theory that the cutaneous manifestations in cases of malignant growth are an expression of the skin's defense mechanism against cancer cells of metastatic origin. Urbach [4] expressed the belief, on the other hand, that this type of eruption is a clinical manifestation of an autoendogenous allergy, the endogenous allergen being a diseased tissue, in this case a malignant neoplasm. He cited an example of an urticarial exanthem in a 70 year old patient with carcinoma of the rectum, whose eruption disappeared after removal of the neoplasm. Other examples of endogenous allergies are those due to altered cutaneous proteins, such as the disseminate eruptions which sometimes follow irritating local treatment of varicose ulcers or severe scratching of hypostatic eczema. Smith [5] called the offending agent in these disorders a dermolysin, which he defined as a foreign protein, probably originating with the breakdown of tissue, to which the patient becomes sensitive and which acts as the trigger mechanism that fires the systemic outbreak.

Another interesting feature in the patient whose case is reported here was the complete disappearance of all bullae several weeks after the institution of high voltage radiation therapy. Urbach,[4] in discussing hormonal endogenous allergy, described a case of dermatitis dysmenorrheica with flares before and during the menstrual period. After temporary castration with roentgen rays there was a complete remission. According to some observers, roentgen rays possess the ability temporarily to desensitize the skin. This observation, in addition to the manner of response to roentgen rays in the present case, further strengthens the possibility of an autoendogenous allergy as the cause of the cutaneous manifestations.

SUMMARY

A case of primary carcinoma of the penis with rapid, early metastasis and a concomitant generalized bullous eruption is presented. There was a history of two previous episodes of bullous eruptions, lasting six months and one and one-half months, respectively. The possibility of pemphigus could not be entirely eliminated, but the changes seen microscopically in a section from a cutaneous lesion and the history and clinical appearance favored the diagnosis of a toxic bullous eruption secondary to malignant growth. High voltage radiation therapy was apparently responsible for the complete involution of the cutaneous lesions but had no inhibitory effect on the rapidly growing and metastasizing tumor. The suggestion is offered that the process causing the eruption may have been an autoendogenous allergy.

1311 Hamilton Street.

4. Urbach, E.: Endogenous Allergy, Arch. Dermat. & Syph. **45**:697-722 (April) 1942.

5. Smith, S. W.: Eczema Autolytica, Brit. M. J. **1**:628-629 (May 5) 1945.

RINGWORM OF THE SCALP DUE TO MICROSPORUM AUDOUINI DURING PREGNANCY

FRITZ B. REIF, M.D.
NIAGARA FALLS, N. Y.

In 1925 Fox and Fowlkes [1] described 3 cases of ringworm of the scalp (tinea capitis) in adults. A review of the literature by these authors revealed about 70 similar cases in Europe and America. A good deal of effort has been spent since that time to discover the cause of nature's spontaneous cure at puberty and the high degree of immunity of adults to the type of ringworm of the scalp caused by Microsporum audouini. In 1946 Rothman and his co-workers [2] identified the fungicidal activity of sebum as residing in the saturated fatty acids, and this problem is apparently near its solution.

The following case of infection of the scalp with M. audouini seems worthy of report because it occurred during pregnancy. I have found no mention of a similar case.

REPORT OF A CASE

L. M. R., an 18 year old Negro woman, complained of a bald spot on her scalp, which she had observed about a month previous to my examination. The lesion was localized on the lower part of the occiput and consisted of a single, roughly rectangular, scaly patch (3 by 5 cm.), without redness or pustules but showing many broken hairs. Examination under the Wood light revealed fluorescent hair stumps of a bright, pale green. The rest of the scalp appeared normal. The microscopic examination of infected hair prepared with a solution of potassium hydroxyde, showed the hair to be covered with sheaths of small spores "like a twig coated with glue rolled in fine sand," to use Darier's description. Infected hair sent to a laboratory for culture yielded a growth of M. audouini.

The source of infection was the scalp of her 12 year old brother, with whom she shared the bed. This boy had a severe ringworm infection over the entire scalp and was treated with roentgen ray epilation.

The patient was treated with intraderm T.C.A.P. solution® (trimethyl cetyl ammonium pentachlorphenate), and she was advised to make three applications daily. Four days after the examination she went to the hospital for her delivery. I saw her three weeks later for the second time and still found fluorescent hair, but the affected area was swollen and showed pustulation. The treatment was changed to the application of hot compresses with diluted solution of aluminum acetate N. F. (Burow's solution). When the patient came back after a lapse of two months, the lesion showed no fluorescence and the examination for fungi gave negative results; hair growth was sparse. The patient refused stubbornly to wash her scalp because of a superstition according to which a mother who washes her scalp before the baby is 6 months old is going to die soon. In spite of that fact neither her baby boy nor her 47 year old husband showed any signs of infection. Two months later the scalp of the patient appeared completely normal.

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1. Fox, H., and Fowlkes, R. W.: Ringworm of Scalp in Adults, Arch. Dermat. & Syph. **11**:446-465 (April) 1925.

2. Rothman, S.; Smiljanic, A. M., and Weitkamp, A. W.: Science **104**:201-203 (Aug. 30) 1946.

SUMMARY

Owing to close contact an infection with M. audouini was transmitted to the scalp of an 18 year old pregant Negro woman. Despite uncleanliness and irregular treatment the infection remained localized and healed within three months.

D. K. Miller, M.D., of the Edward J. Meyer Memorial Hospital of Buffalo, N. Y., made the culture.

Pine Avenue and Main Street.

CONTACT DERMATITIS FROM STREPTOMYCIN

SAMUEL J. LEVIN, M.D.
AND
SELMA S. MOSS, M.D.
DETROIT

The introduction of a new drug is followed frequently by reports of sensitivity. Such was the case with the sulfonamide drugs and, more recently, with penicillin. Streptomycin, the most recent of the antibiotic drugs to come into widespread use, has already been the subject of reports on cutaneous eruptions which, in some patients, have followed its injection.[1] The cutaneous eruptions following the administration of streptomycin are apparently much like those seen after treatment with penicillin and are urticarial or generalized macular, maculopapular or morbilliform. Contact dermatitis from penicillin has also been reported.[2] It is therefore not unexpected that sooner or later a case of contact dermatitis from streptomycin should be encountered. The case described here is apparently the first of this type to be reported.

REPORT OF A CASE

Mrs. A. J., aged 42, a graduate nurse, was employed in a hospital for tuberculous patients. A severe eruption of the face and neck, requiring her to discontinue her duties, developed. The eruption disappeared after one week, and the patient was able to return to work. A similar but much more violent eruption reappeared within a few days and again necessitated her stopping work.

Examination revealed a very severe acute dermatitis of the face and neck, with pronounced edema of the eyelids. The eruption was extremely pruritic, and in sev-

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1. Hettig, R. A., and Adcock, J. D.: Toxicity of Streptomycin for Man: A Preliminary Report, Science **103**:355-357 (March 22) 1946. Heilman, D. H.; Heilman, F. R.; Hinshaw, H. C.; Nichols, D. R., and Herrell, W. E.: Streptomycin: Absorption, Diffusion, Excretion and Toxicity, Am. J. M. Sc. **210**:576-584 (Nov.) 1945. Keefer, C. S.: Streptomycin in the Treatment of Infections: A Report of One Thousand Cases, J. A. M. A. **132**:70-76 (Sept. 14) 1946. Zintel, H. A.; Flippin, H. F.; Nichols, A. C.; Wiley, M. M., and Rhoads, J. E.: Studies on Streptomycin in Man: I. Absorption, Distribution, Excretion and Toxicity, Am. J. M. Sc. **210**:421-430 (Oct.) 1945. Steiner, K., and Fishburn, G. W.: Cutaneous Eruptions from Streptomycin, Arch. Dermat. & Syph. **56**:511-512 (Oct.) 1947.

2. Friedlaender, S.; Watrous, R. M., and Feinberg, S. M.: Contact Dermatitis from Penicillin: Source of Antigen, Arch. Dermat. & Syph. **54**:517-523 (Nov.) 1946.

eral areas there were weeping and excoriation. It was discovered on questioning the patient that one of her duties consisted in the administration of streptomycin hypodermically to tuberculous patients. Patch tests were carried out for all the substances used in her work, including streptomycin, the tests using the concentration of these substances normally employed. The tests gave negative reactions, with the exception of that with the streptomycin solution, which gave within twenty-four hours a 4 plus reaction requiring more than one week to disappear. The patient returned to her work in the hospital with the advice that she avoid contact with streptomycin. At the time of writing, several months after she had begun to avoid contact with this substance, she had remained free of dermatitis.

SUMMARY

A case of contact dermatitis due to streptomycin is reported. The patch test with this agent a strongly positive reaction. Reexposure produced a relapse, and, at the time of writing, avoidance of contact has kept the patient free of symptoms for several months.

NOTE.—When this paper was submitted, no other cases of contact dermatitis from streptomycin had been reported. Since then, several observers have reported a number of additional cases of a similar condition, occurring in nurses handling this material.

469 Fisher Building (2).

SOLID CARBON DIOXIDE THERAPY FOR CYSTIC ACNE

CARROLL S. WRIGHT, M.D.
AND
E. R. GROSS, M.D.
PHILADELPHIA

In March 1941 Eller and Wolff[1] suggested cryotherapy, or the use of carbon dioxide slush, in the treatment of recalcitrant cases of acne vulgaris and its scars. After this report, we began to use carbon dioxide slush in the treatment of severe and scarred lesions of acne vulgaris but found the method unwieldy and not particularly helpful in removing or improving the scars. It was observed, however, that cystic lesions would almost invariably disappear after a few treatments, and so we conceived the idea of using simply a pencil or block of solid carbon dioxide, or dry ice,® for the treatment of cystic acne. The results in the treatment of more than 2,000 patients with cystic or severe acne vulgaris have been so good that we have given up the surgical treatment of deep-seated acne lesions, which, we feel, increases scar formation.

The procedures we have used are as follows:

1. Carbon dioxide gas is collected from an inverted tank in a piece of soft chamois bound firmly to the nozzle of the tank or to an especially made tip that will screw onto the nozzle. The resulting cold solid may be shaved

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From the Department of Dermatology, Temple University School of Medicine.

1. Eller, J. J., and Wolff, S.: Skin Peeling and Scarification in the Treatment of Pitted Scars, Pigmentations and Certain Facial Blemishes, J. A. M. A. **116:** 934-938 (March 8) 1941.

into pieces the size of an average cystic acne lesion, or the entire block may be used.

2. The Kidde apparatus may be used, the solid carbon dioxide being collected in one of the sleeves provided with the apparatus.
3. If available, dry ice® may be cut into appropriately sized pieces.

The application of the solid carbon dioxide may be made directly to the acne pustule, moderate pressure being used, for from three to five seconds; or, if the acne lesions are numerous, a large block may be applied over a group of lesions at one time. Since the lesions are usually elevated, the intervening areas of skin are untouched unless the pressure is too firm.

Within a few hours there may be surface vesiculation over the pustule, which development should always be explained to the patient. This is followed by drying and a general shrinkage of the treated pustules, which will usually result in their involution in from one to two treatments, with little or no scarring. Deep cystic lesions may require a number of treatments, the number depending on their depth.

Some of our patients have been observed for as long as six years, and there have been no untoward after-effects. Carbon dioxide slush is difficult to handle, but the block or pencil of solid carbon dioxide is handled very simply. (If desired, the block or pencil may be lightly moistened with acetone.)

1402 Spruce Street (2).

LEAD-CONTAINING CLAY FOR SHIELDING IN ROENTGEN RAY TREATMENT OF THE SKIN

ROBERT KALDECK, M.D.
LOWELL, MASS.

The conventional means employed for shielding the skin from roentgen rays is lead foil or rubberized lead sheet. When small areas of the skin are treated with intensive doses, the protection of the remaining areas has to be very accurate. The cutting of those materials to an exact size is time consuming and often difficult. If a shield is too large or cannot be corrected in form, another one has to be made.

Rubberized lead and lead foil are stiff materials, which do not fit closely elevations and depressions; on the face and on the fingers particularly, they tend to move, even after having been fastened with adhesive tape. There is need for a plastic material that does not have these disadvantages.

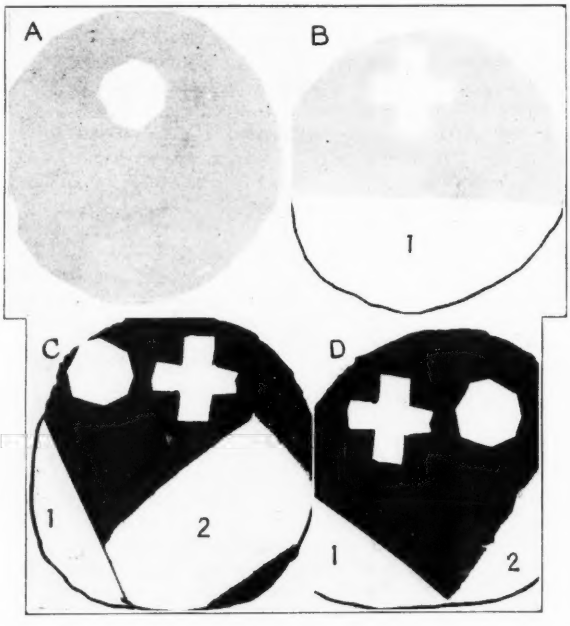
A lead-containing clay was compounded, as follows:

	Per cent (by weight)
Fine lead powder	77
Petrolatum U.S.P.	9
Plastic clay (as used in toy sets)	5
Talcum powder	9

The mass is lead gray, nonsticky, slightly harder than soft putty, easily molded at room temperature, nonelastic and nonresilient. With the use of a round pencil as a rolling pin, any thickness can be produced easily. Then an opening the approximate shape of the area to be treated is cut out with a pocket knife. After application of the clay to the skin the opening is checked and desired changes are made by slight pressure with the fingers or any instrument at hand. When a treatment cone with a large opening is used, lead foil or rubber with an opening larger than that desired can be employed and clay can be used to narrow the opening to the desired form.

In order to test the shielding ability of the compound, photographic print paper in sealed cardboard envelopes was exposed to roentgen rays, and portions of the field were covered with different thicknesses of the clay. The distance from the tube was 4½ inches (11.5 cm.), and the voltage was 85 kilovolts. Markers cut from 1/16 inch lead foil were used to identify the fields, and comparison of the protective ability against roentgen rays was made with 1/16 inch rubberized lead sheet (General Electric Co.).

The tests showed that a 1/16 inch (1.5 mm.) thickness of the clay has protective power equal to that of the same thickness of lead foil or rubberized lead. However,



Demonstrations of the shielding ability of various materials. *A*, empty field with marker, exposed to 75 r, 85 kilovolts, at a 4½ inch (11.5 cm.) distance. *B*, field exposed to 75 r, 85 kilovolts, at a 4½ inch distance. *C*, field exposed to 2,000 r, 85 kilovolts, at a 4½ inch distance. *D*, field exposed to 3,000 r, 85 kilovolts, at a 4½ inch distance. In *B*, *C* and *D*, *1* indicates the area shielded by 1/16 inch (1.5 mm.) rubberized lead shield, and *2*, that portion protected by 1/16 inch lead clay.

for easier handling, a 3/16 inch (4.5 mm.) thickness of the clay is recommended, which thickness means an according increase in safety. The advantages of the compound are these: A saving in time and material and greater accuracy and safety in the shielding of small lesions, particularly those under intensive treatment and on curved locations.

174 Central Street.

CONCURRENT FUNGOUS INFECTION OF THE SKIN

Report of a Case

EDWARD P. CAWLEY, M.D.
AND
S. F. HORNE, M.D.
ANN ARBOR, MICH.

The relative infrequency of cutaneous infections caused by Trichophyton violaceum, in addition to the supposed rarity of multiple fungous infections of the skin, emphasizes salient features of the case reported here, which is, insofar as can be determined, the original recorded observation of a simultaneous infection with T. violaceum and Trichophyton gypseum. Seventy-three previous examples of multiple fungous infection of the skin are to be found in the literature.

In a recent report, Lewis and Hopper [1] defined "concurrent infection" as the simultaneous presence on different parts of the body of two or more species of pathogenic fungi which are causing mycotic infections of the skin and are unrelated clinically and immunologically. "Combined infection" refers to the condition in which isolation of two or more different species of fungi from the same area of skin leads one to suspect a clinical and/or immunologic interrelation, while "consecutive infection" has reference to cases in which "a fungous infection due to one pathogen clearly antedated a second fungous infection due to a species different from the first."[1] Out of 400 cases of proved fungous infections (established by positive culture and/or direct mount) found by Lewis and Hopper during a two year period, there were 19 (3 doubtful) cases of concurrent infection. In addition, there were 9 (5 doubtful) cases of consecutive infection and only 1 of the combined type. This observation indicates that in 7.2 per cent of the cases of fungous infection of the skin multiple organisms were believed to have been causative and that 5.25 per cent of the cases were undoubted examples of multiple mycotic infections of the skin.

In 1941, Muskatblit [2] was able to find in the literature only 36 cases of multiple fungous infections of the skin, to which number he added 6 cases. Lewis and Hopper [1] stated the belief that multiple fungous infections are not uncommon and that more cases would be found if proper laboratory studies were made. We are in agreement with both points but have been able to find only 2 recorded cases[3] since the report of these workers, the total now being 73 cases in the literature.

REPORT OF CASE

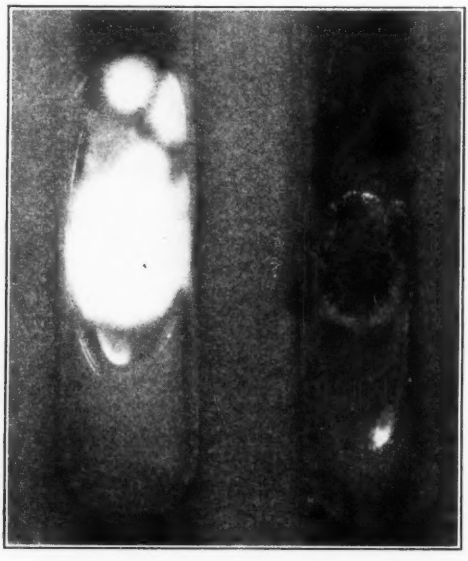
Z. M., a 55 year old white woman, was seen in the medical clinic of the University Hospital on July 14, 1947. After an extensive study of the case, a

1. Lewis, G. M., and Hopper, M. E.: Concurrent, Combined and Consecutive Fungous Infections of the Skin, Arch. Dermat. & Syph. **47**:27 (Jan.) 1943.

2. Muskatblit, E.: Combined Fungous Infections: Report of Six Cases with a Review of Thirty-Six Cases from the Literature, Arch. Dermat. & Syph. **44**:631 (Oct.) 1941.

3. Bereston, E. S., and Waring, W. S.: Onychomycosis and Dermatomycosis caused by Trichophyton Rubrum and Aspergillus Nidulans, Arch. Dermat. & Syph. **52**:162 (Sept.) 1945. Muskatblit, E.: Dermatophytosis Due to Combined Infection with Trichophyton Interdigitale and Trichophyton Purpureum: Report of a Case, ibid. **54**:588 (Nov.) 1946.

diagnosis of conversion psychoneurosis, hypertensive vascular disease and obesity was made. The patient was referred to the dermatologic clinic on July 31 because of a puritic erythematous lesion on the forehead which had appeared every summer for four years and had cleared spontaneously each winter, and because of brittleness and deformity of the finger nails which had been present for "many years" (at least ten). Examination revealed discoloration, deformity and brittleness of all the finger nails and a raised, erythematous, scaly, gyrate lesion across the forehead. Direct mount from the cutaneous lesion and from



Photograph of the original cultures, showing that of Trichophyton violaceum on the right and that of a granular variety of Trichophyton gypseum on the left.

the nails revealed a large number of myceliums. A culture made from the lesion on the face showed a granular variety of T. gypseum, and one from a finger nail, a typical T. violaceum (figure). Treatment of the lesions with a fungicidal ointment produced rapid clearing of the lesion on the face but had no apparent effect on the infected nails. The patient has not returned since approximately two weeks after the first visit.

SUMMARY

A case of concurrent fungous infection of the skin is reported (the original observation of concurrent infection with T. gypseum and T. violaceum), and multiple fungous infections of the skin are briefly reviewed.

Department of Dermatology, University Hospital.

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*Cecil, R. A.: A Textbook of Medicine. Philadelphia, W. B. Saunders Co., 1947, p. 376.

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*Stillians, Arthur W.; Concealment of Cutaneous Blemishes, Arch. Derm. & Syph. 57: 279 (Feb.), 1948

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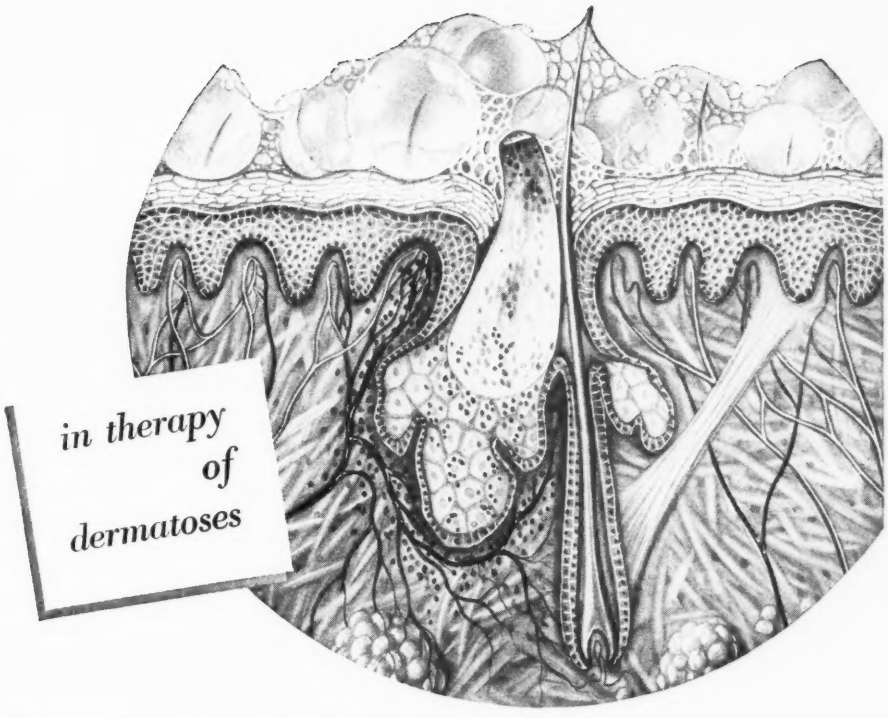

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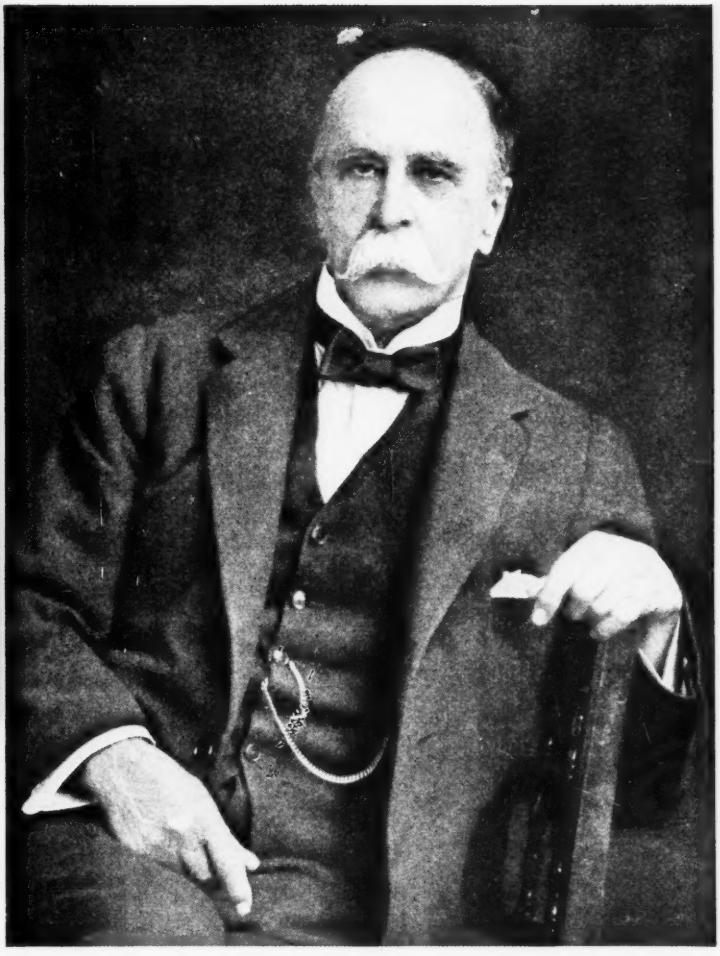

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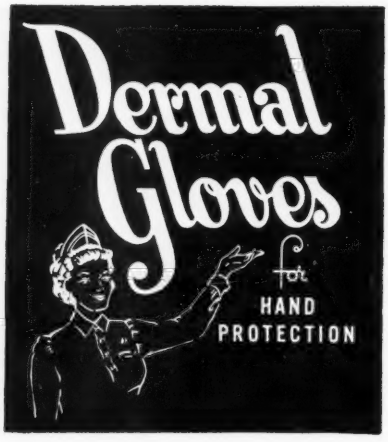

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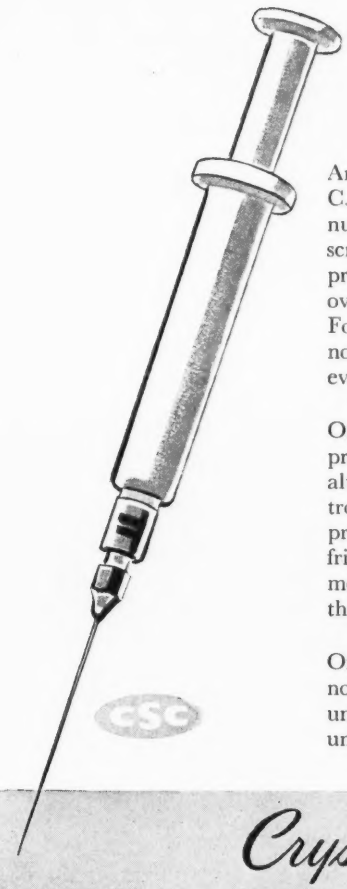

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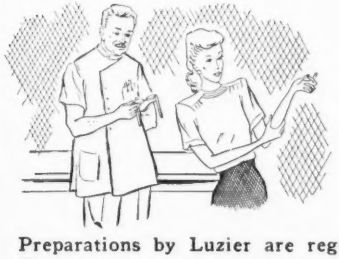

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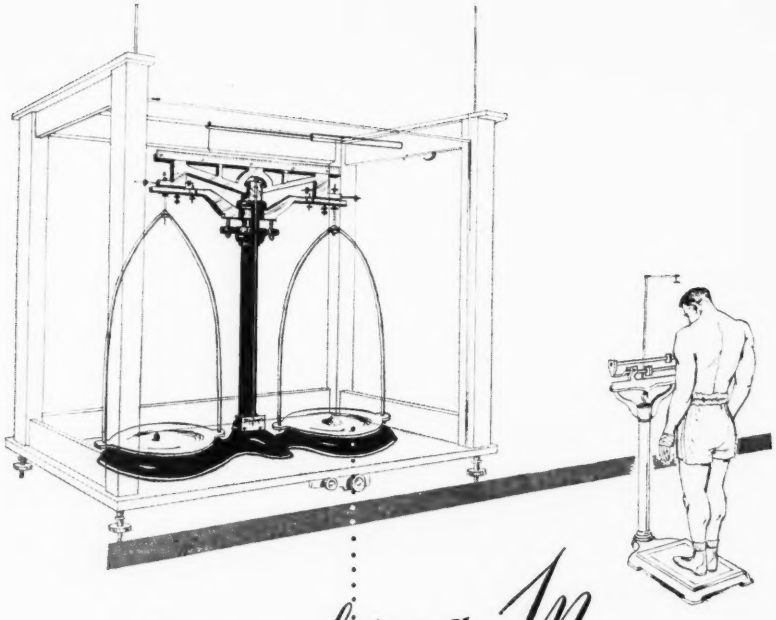

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